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Review

Epistemology of the Origin of Cancer III: Fundamentals of How Metastasis Arises

Björn L. D. M. Brücher[a,b,c,d] Ijaz S. Jamall[a,b,c]

[a]European Academy of Sciences and Arts (EASA), Salzburg, Austria [b]Theodor-Billroth-Academy® with its INCORE, International Consortium of Research Excellence, Munich, Germany, Sacramento, CA, USA, [c]Cancer Metastases Research Fund, Sacramento, California, United States of America, [d]Department of Surgery, Medical University Lausitz – Carl-Thiem, Cottbus, Germany

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Abstract
Metastasis, like carcinogenesis, involves the disruption of homeostasis such that cancer cells travel from the primary tumor to distant parts of the body. Almost all cancer deaths are due to metastatic spread. The prevailing theory of metastasis is an incomplete doctrine and far from sufficient as only 0.2% of free cancer cells result in the spread of cancer. To develop reasonable and effective cancer therapies and to prevent (or reverse) carcinogenesis and metastasis, a comprehensive understanding of how both carcinogenesis and metastasis arise is necessary. Fundamental questions in cancer biology have been asked and answered over decades of research: *How do most cancers develop* (Epistemology of the Origin of Cancer I, 2014–2022)? *Which is the first cancer cell* (II, 2023)? The third basic question in cancer biology remaining to be addressed is: *What are the fundamentals of how metastasis develops?* The pre-cancerous niche (PCN) that forms during carcinogenesis is altered by ongoing complex signaling into a premetastatic niche 1 (PMN-1): p130(cas)/crk/DOCK180 formation is necessary for lamellipodia formation, thereby enabling cell mobility. Cancer-associated fibroblasts (CAFs) begin to release fibronectin CXCL12 and Keratin 19. PMN-1 is transformed into PMN-2 during ongoing crosstalk and transformation of anti- into pro-tumorigenic platelets, macrophages, and neutrophils. Finally, persistent signaling and immune evasion result in the conversion of PMN-2 to PMN-3 with heterogeneous cancer satellites – the term "satellite" is used herein in accordance with its original meaning (a cell or particle escorting another). PMN-3 serves as a prerequisite for intravasation, traveling, and dissemination of cancer cells away from the primary tumor. Eight heterogeneous cancer satellites, including Trojan horses (immune evasion), travel alone or in combination: (1) cancer cells and (2) CAFs migrate along the CXCL12 and fibronectin gradient; (3) cancer cells surrounded by CAFs are shielded from the immune system and travel away from the primary cancer; (4) CXCL12 and Keratin 19 coat cancer cells; (5) platelets surround cancer

Björn L. D. M. Brücher
Department of Surgery, Medical University Lausitz – Carl-Thiem, Cottbus, Germany
E-Mail: b.bruecher@mul-ct.de

cells and (6) CAFs, thereby facilitating cancer spread; and (7) neutrophil extracellular traps shield cancer cells and (8) CAFs. Metastasis in epithelial cancer occurs in parallel with carcinogenesis after the pre-cancerous niche is transformed into pre-metastatic niches (PMNs), which are indispensable to the origin of metastasis. Eight heterogeneous cancer satellites, including Trojan horses responsible for immune evasion, alongside reciprocally affecting sequences, wander alone or in conjunction with other cancer cells. This elucidates why the current practice of multimodal anti-cancer cell therapy should now be seen in a new light in which the benefits depend not on direct cancer cell effects, but on indirect cytopenic effects, which have previously been regarded merely as adverse effects.

Introduction

Homeostasis is a fundamental biochemical and physiological regulatory process that maintains a balance of all systems within the body, thereby sustaining a state of health. Homeostasis is an equilibrium state and a law of nature, without which no life would be possible. When the homeostatic balance is disrupted, diseases begin to develop. A simple analogy for homeostasis is the ability of a rubber band to be stretched and return to its original shape and size when released, but to break when stretched too far. This analogy of breakage applies to homeostasis in chronic diseases such as cancer. In science, homeostasis has largely been ignored in the understanding of disease processes [**1**].

The disruption of homeostasis, in all its complexity, is a hallmark of cancer and metastasis. Because homeostasis is critical for maintaining health, nature maintains homeostasis through multiple routes, such that biochemical and physiological redundancies protect against disease and enable health. More detailed information on homeostasis is provided in the supplemental material (Supplement part 1, Homeostasis).

To achieve homeostasis, cells must "talk" to one another to gain information on what is happening in their own neighborhood and across the living organism. This process is referred to as cell-cell communication, which has been described as "*the music that the nucleus hears*" [**2, 3**]; moreover, "*biological processes as well as cell-cell communication and signaling are themselves a multidimensional musical opera in different acts, which are played differently by different symphony orchestras rather than by a soloist*." Additionally, as a colleague of ours stated, there is a lot of music, which is too fast to be heard by the nucleus.

Cancer involves the disruption of homeostasis, including dissonant and aberrant cell-cell communication. Most cancers (80.5%) are epithelial cancers, which markedly differ in their development, spread, and response to therapy [**4**]; epithelial cancer relapse rates in adults have not changed substantially, and cancer incidence continues to rise and is expected to double by 2070. The absolute (unadjusted) cancer mortality rates have not changed considerably over the past 80 years, although tangible benefits have been achieved in certain subpopulations where cause-based approaches have been adopted; for example, hepatitis C virus-induced liver cancer and human papillomavirus-induced cervical cancer have recently been prevented by vaccines.

Age-adjusted data are useful for comparing potential risks but should not be mistaken for precise measures, particularly when demographics change over long time periods. This important aspect is particularly evident in cancer statistics, wherein relative age-adjusted figures are used to demonstrate progress against cancer but often contradict the absolute cancer mortality rates [**4**]. Even gains in early cancer detection have achieved only small benefits in terms of mortality.

Both clinical and experimental data show that genetics (e.g., mutations), despite having been consistently described as key to understanding and treating cancers and having remained a major cancer research focus, does not explain the cause of most cancers. To date, only approximately 5% of cancers have been demonstrated to be caused by genetic mutations [**5**]. This ongoing focus on mutations explains why approximately *80% of cancers are first diagnosed in advanced stages, and approximately 50% of patients with cancer have*

metastasis at the time of initial diagnosis [**6**]. Somber findings have indicated that cancer incidence, metastasis, and mortality statistics have not changed substantially over the past century [**4**].

The identification of certain somatic mutations like TP53, KRAS, EGFR and others have proven helpful in the treatement of certain epithelial cancer and most notably in the selection of immunotherapeutic agents that work better in patients with such somatic mutations. That said, the application of the mutation theory has, to date, not substantially improved patient survival even though it has improved disease free progression in certain cancers.

One persisting challenge is that no morphological features can be used to distinguish tumorigenic from non-tumorigenic strains [**7**]. For example, no discernible difference in DNA repair exists between normal and pre-neoplastic breast tissues, thus further confirming the minor (or absent) role of somatic mutations as the cause of most cancers [**8**].

A known, yet largely ignored, finding is that genetic mutations do not clinically explain most epithelial cancers, because genes are not merely blueprints containing information [**3**] and do not function as blueprints for life [**9, 10**]. Thus, a "gene delusion" applies to the understanding of most cancers [**11**]. Genome-wide association studies, as part of the Human Genome Project, cost $3 billion from 1988 to 2003 in the U.S. and had an economic impact of approximately $796 billion [**12**] and an estimated economic return to the U.S. economy of $1 trillion [**13**]. But where are the benefits to patients with cancer in terms of quality of life or overall survival, measured in years, not in mere weeks or months, as continually indicated by numerous clinical studies? Despite investments of billions of dollars, the incidence of epithelial cancers is predicted to rise. The development of effective cancer therapies and metastasis prevention can be achieved only with proper etiological understanding.

To help patients most in need, essential cancer biology questions have been asked and answered over decades of research on disrupted homeostasis, including signaling and crosstalk in carcinogenesis: [*1*] How do most cancers develop? (*2*) Which is the first cancer cell?

These two fundamental cancer biology questions were answered by complex research in 2014–2022 (*Epistemology of the Origin of Cancer I*) (**FIGURE 1**) [**3, 14**] and 2023 (*Epistemology of the Origin of Cancer II)* (*Please see figures 1 to 3 in* [**15**]).

Simplified scheme representing ongoing disruption of homeostatic crosstalk. This illustration was originally discussed in the paradigm presented in our prior publication [**3, 14**] and modified in 2019 [***16-19***]. The first four carcinogenesis sequences are included: [1] a pathogenic stimulus is followed by [2] chronic inflammation, thus resulting in [3] fibrosis with associated remodeling of the cellular microenvironment; after these changes, a [4] pre-cancerous niche (PCN) is formed as a product of fibrosis and it's remodeling by lysyl oxidase (LOX) through persistent inflammation.

Finally, CAFs undergo mesenchymal-epithelial transition (MET) and express epithelial markers that facilitate their integration into the target tissue. The continual increase in CAFs ultimately leads to complete and unresolvable disruption of physiologic homeostasis. CAFs then undergo MET, and these cells, which continue to express epithelial markers, become the first cancer cells. The former fibroblasts are then integrated into the epithelium. This neoplastic transformation to a cancerous phenotype also explains the very high heterogeneity of cancers.

Overall cancer mortality rates and rates of metastasis in epithelial cancers have not substantially changed in the past 80 years [**4**].

Metastasis starts soon after the first cancer cell has developed

Readers are referred to the further details regarding many aspects of metastasis complexity and heterogeneity presented in the supplemental materials.

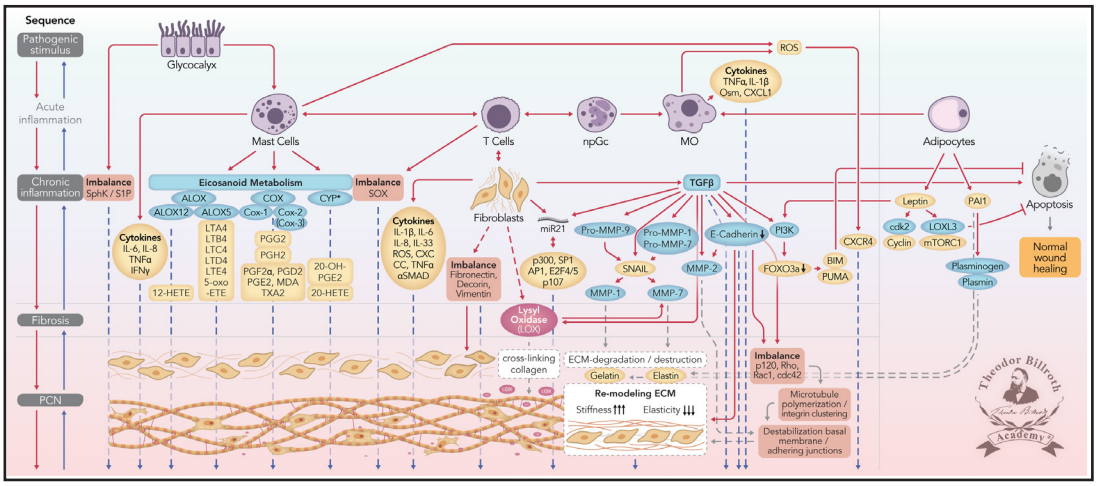

Fig. 1. This Fig. combines findings from prior research [3, 14, 16, 17] with signaling crosstalk, without applying the Chronic Stress Escape Strategy (CSES) and the Normal Cell to Cancer Cell Transition (NCCCT). The nomenclature of common abbreviations is shown in bold and is followed by common names or International Union of Pure and Applied Chemistry (IUPAC) names, as available: PCN: pre-cancerous niche; SphK: sphingosine kinase isoform; S1P: sphingosine-1-phosphate; IL-6: interleukin 6; IL-8: interleukin 8; TNFα: tumor necrosis factor alpha; IFNγ: interferon gamma; ALOX: lipoxygenase, arachidonate lipoxygenase; ALOX12: 12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type; ALOX5: 5-lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase; 12-HETE: 12-hydroxyeicosatetraenoic acid; LTA4: leukotriene A4, 4-[(2S,3S)-3-[(1E,3E,5Z,8Z)-tetradeca-1,3,5,8-tetraenyl]oxiran-2-yl]butanoic acid; LTB4: leukotriene B4, (5S,6Z,8E,10E,12R,14Z)-5,12-dihydroxyicosa-6,8,10,14-tetraenoic acid; LTC4: leukotriene C4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-[[(4S)-4-amino-4-carboxybutanoyl]amino]-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid; LTD4: leukotriene D4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid; LTE4: leukotriene E4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-2-carboxyethyl] sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid; 5-oxo-ETE: (6E,8Z,11Z,14Z)-5-oxoicosa-6,8,11,14-tetraenoic acid; Cox: cyclooxygenase; Cox-1: cyclooxygenase 1; Cox-2: cyclooxygenase 2; Cox-3: isoform of Cox-2 (therefore in brakes); PGG2: prostaglandin G2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroperoxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; PGH2: prostaglandin H2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; PGFF2α: prostaglandin F2 alpha, (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl] hept-5-enoic acid; PGD2: prostaglandin D2, (Z)-7-[(1R,2R,5S)-5-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid; PGE2: prostaglandin E2, (Z)-7-[(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid; MDA: malondialdehyde, propanedial; TXA2: thromboxane A2, (Z)-7-[(1S,2S,3R,5S)-3-[(E,3S)-3-hydroxyoct-1-enyl]-4,6-dioxabicyclo[3.1.1]heptan-2-yl] hept-5-enoic acid; CYP*: cytochrome P450 isoforms; 20-OH-PGE2: 20-hydroxy prostaglandin E2; 20-HETE: 20-hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,14Z)-20-hydroxyicosa-5,8,11,14-tetraenoic acid; SOX: [sex-determining region Y (Sry) box-containing] transcription factor family; IL-β1: interleukin beta 1; IL-33: interleukin 33; ROS: reactive oxygen species; CXC CC: chemokine receptors; αSMAD: alpha-smooth muscle actin; miR21: microRNA-21; p300: protein 300 (p300-CBP coactivator family); SP1: specificity protein 1; AP1: activator protein 1; E2F4/5: cytoplasmic complex of Smad3, retinoblastoma-like protein 1 (P107, RBL1), E2F4/5 and D-prostanoid (DP1); p107: retinoblastoma-like protein 1, RBL1; TGFβ: transforming growth factor beta; Pro-MMP-9: pro-matrix metalloproteinase 9; Pro-MMP-1: pro-matrix metalloproteinase 1; Pro-MMP-7: pro matrix metalloproteinase 7; SNAIL: zinc finger protein SNAI1; MMP-1: matrix metalloproteinase 1; MMP-7: matrix metalloproteinase 7; MMP-2: matrix metalloproteinase 2; E-cadherin: CAM 120/80 or epithelial cadherin, cadherin-1, epithelial cadherin; CXCL1: chemokine (C-X-C motif) ligand 1; Osm: oncostatin-M; PI3K: phosphatidylinositide 3-kinase; FOXO3a: forkhead box protein O3a; p120: catenin delta-1, protein 120; Rho: Ras homolog gene family, member A; Rac1: Ras-related C3 botulinum toxin substrate 1; cdc42: cell division control protein 42 homolog; BIM: Bcl-2 interacting mediator of cell death; PUMA: BH3-only protein; CXCR4: C-X-C motif of chemokine receptor 4; cdk2: cyclin-dependent kinase 2; LOXL3: lysyl oxidase homolog 3; mTORc1: rapamycin complex 1; PAI1: plasminogen activator inhibitor-1.

The injection of radiolabeled cancer cells were found to result in only 0.1–0.2% of the cells becoming metastatic [**20**]. The lack of change in metastatic rates in recent decades suggests that the origins and development of metastasis must differ from the prevailing understanding. Therefore, a third fundamental question in cancer research that remains to be answered is: *What are the fundamentals of how metastasis occurs?*

Herein, we provide potential explanations of the fundamentals of how metastasis arises in epithelial cancers. Our findings are concordant with clinical, scientific, and experimental findings, which together demonstrate the diversity of metastatic patterns. Deciphering these metastatic patterns requires an in-depth understanding of complex signaling and crosstalk.

Metastasis

Metastasis comes from the Greek term μετάστασις, meaning migration or displacement. In cancer, this term describes the secondary cancers that occur in areas of the body distant from the primary cancer. Therefore, cancer cell formation is temporally followed by metastasis.

Henry Earle (1789–1838), in 1823, reported that local irritation was the reason for many cancers and their spread [**21**]. Several years later, in 1829, Joseph-Claude-Anthelme Récamier (1774–1852) first used the term "metastase" (metastasis), in a report of a case of breast cancer with brain metastasis [**22** *reviewed in* **23**].

The supplemental material provides detailed information regarding proposed models of metastasis (various vascular hematogeneous lymphatic theories and their combination, such as the embolic theory; preliminary work and the subsequent development of seed and soil theory; and cancer implantation models) (Supplement, part 2, Metastasis theories); metastasis models (Supplement, part 3, Metastasis models); and metastasis injection models (Supplement, part 4, Metastasis injection models).

This knowledge is indispensable for understanding the biology of cancer and the origins of metastasis, but still is incomplete. The prevailing wisdom in cancer research is that circulating cancer cells are the main source of metastasis. We discuss those data underlying these theories of metastasis and show why they are insufficient to explain the spread of cancer from the primary tumor to distant sites.

Circulating tumor cells

Circulating tumor cells (CTCs) consist of red blood cells (erythrocytes), white blood cells (leucocytes), lymphocytes (antibody producing B- and T-cells), monocytes and macrophages, dendritic cells (type 2 dendritic cells and plasmacytoid dendritic cells), basophils, and platelets. CTCs have been used to explain the detection of cancer cells in circulation (a correct observation but an incorrect interpretation) [**24, 25**] as follows: epithelial cells break through the basal membrane; enter vascular structures (veins, arteries, and lymphatic vessels); are carried away by the blood and lymph streams; and implant elsewhere, thus giving rise to metastasis. However, *detection of cancer cells in the blood is not synonymous with cancer dissemination*, despite widely being accepted as such. The data disproving the CTC theory is discussed below.

In prior studies, highly aggressive cancer cells were cultivated [**20, 26**], and all inoculated cells were radiolabeled with ^{125}I-iodo-2´-deoxyuridine (^{125}IUDR). Immediately after injection, most cancer cell emboli arrested within the lungs, and a few very rarely entered the pulmonary circulation. Within 24 hours, less than 1% of cancer cells survived. After 2 weeks, only *0.2%* of cancer cells injected into the bloodstream (400 of 200, 000) had survived in the lungs. No injected cancer cells survived in the liver, spleen, kidney, blood, or urine. Notably, only a small number of patients with disseminated tumor cells and CTCs develop clinically evident metastatic cancer [**27**]. Consequently, most (99.8%) cancer cells in the bloodstream

do not survive to cause metastasis [**20, 26**]. Injected ^{125}I-iodo-2´-deoxyuridine (^{125}IUDR)-labeled cancer cells killed by heat or radiation showed no radioactivity in the lungs 8 hours later. Injecting the same cells without inactivation revealed that 24 hours post-injection, no radioactivity was evident.

These data reveal that the efficiency of the immune system and the limitations of the seed and soil-theory of CTCs. A cancer nodule of 1 cm contains 1 billion cells (1, 000, 000, 000 cells, 10^9 cells), only 1 million of which (1, 000, 000 cells, 10^6 cells; *0.1%*) can be shed into the circulation per day. However, injection of 2×10^6 cells (2, 000, 000 cells) per animal rarely resulted in lung metastasis [**28**]. These data demonstrate that the existing explanations for how metastasis occurs are incomplete, and approximately 99.8% of metastasis occurs through a different route(s).

Moreover, a similar increase in CTCs was observed in a different experiment: induced peritoneovenous shunts aimed at decreasing malignant ascites and improving quality of life in patients with ovarian cancer, caused millions of cancer cells to enter the bloodstream but did not increase metastasis [**29, 30**]. Various terms are used to describe CTCs, including clusters, microemboli, and collective tumor cell migration with high metastatic potential [**31, 32**]. Additional information regarding CTCs is provided in the supplemental material (Supplement, part 5, Circulating tumor cells).

Clinical findings

Clinical findings for metastases are heterogeneous, given the distinct microenvironments of cancers across different organs [**6**, **20**, **23**, **30**].

Various epithelial cancers, such as those from the ovaries, colon, pancreas, rectum, and stomach, heterogeneously spread to the lymph nodes, liver, and lungs, and subsequently the peritoneum. Furthermore, pancreatic and gastric cancers are upper gastrointestinal cancers without major venous flow through the inferior mesenteric vein. Esophageal cancer, despite its location and histology (adenocarcinoma versus squamous cell carcinoma), can spread to the lymph nodes, lungs, liver, bones, and peritoneum. In contrast, breast cancers preferentially metastasize to the bones, followed by the brain, liver, and lungs. Prostate and kidney cancers metastasize to the adrenal glands, bones, lymph nodes, liver, lungs, and brain. Bladder, thyroid, and uterine cancers preferentially spread to the bones, liver, and lungs.

Lymph node metastasis in primary breast cancer occurs in approximately 30–50% of cases [**33, 34**]. A higher likelihood of lymph node metastasis is associated with age (particularly younger age in women), race (particularly Black), primary site (particularly the upper-outer quadrant), histology (particularly lobular carcinoma), breast subtype (particularly HR−/Her2neu+), grade (particularly grade 3), and T-stage (particularly the T3 category). Tumor size (in 10 mm increments), lymph nodes, and distant spread do not demonstrate linear relationships, thus suggesting that larger tumors do not necessarily spread to distant organs or the lymphonodular regions [**35**]. This is in agreement with findings in other epithelial cancers, in which T4 (larger) cancers do not always demonstrate metastasis.

Lymph node metastasis in animal models aids in understanding the time course of metastasis. Lymphatic spread was found to occur as early as the 4th day after tumor transplantation in a mouse model [**36**]. In the stage of nidation, no metastasis occurred. Therefore, lymph node metastasis occurs early [**37**] and after non-visible cancer spread. Dormancy of cancer cells can be considered a rule rather than an exception.

Friedrich Stelzner (1921–2020) showed that a sharp separation of hematogenous venous metastases between the portal vein and the cava system is not possible because of a network of natural short-circuit anastomoses [**38**]. Furthermore, if lymphatic drainage were the major route of lymphatic cancer spread, several questions should be asked, including why patients undergoing esophagectomy for esophageal squamous cell carcinoma (ESCC), including thoracic duct resection, have a 4% higher rate of distant metastasis [**39, 40**].

Large colon carcinomas result in metastasis less often than moderately sized or small cancers, as shown in a study of 3, 000 colorectal cancers (CRCs) [**41**]. This finding has been widely reported [**42**], but has been disproven, given that Frederick Allen Coller (1887–1964), approximately 85 years ago, demonstrated that lymph node metastasis occurs at higher rates in smaller rather than larger bowel cancers [**43**]. However, in breast cancer, greater tumor size is associated with more metastatic lymph nodes.

These observations indicate that not only the size of the primary tumor but also the organ where the primary cancer occurs determines metastatic potential. This suggests that signaling and crosstalk biology, which have not been considered as necessary so far, seem to play a much more important role.

In a prostate cancer study, approximately 33% of bone metastases were observed in the sternum and ileum, but only 9% showed widespread bone metastases [**44**], thus indicating that the distribution of these metastases could not be explained by vascular theory.

Intravenous inoculation of radiolabeled CRC cells showed 66% lymph node metastasis, thereby suggesting that venous vascular cancer cell inoculation was responsible for more than two-thirds of the spread into the lymph nodes [**45**].

According to the *Fuchs-Paget seed and soil* theory [**46, 47**], cancer cells (the "seed") are distributed through the vascular system, and metastases can develop only in locations with favorable conditions (the "soil"). Ewing, in 1928, also suggested that cancers spread to areas where the vascular system (blood and lymphatics) allows them to travel [**48**]. Although early cancer surgery was long believed to prevent metastasis, clinical data have revealed that even after one or two decades, patients with epithelial cancer can develop heterogeneous metastasis [**15, 49**], and animal studies have demonstrated that such lesions can lead to metastatic spread [**50**].

A study of 213 CRC cases has examined hypermutable DNA regions and/or conducted phylogenetic analysis to elucidate the origins of lymphatic or distant metastasis [**51**]. In approximately 65% of cases, lymphatic and distant metastases arose from independent subclones in the primary tumor, and only 35% of cases shared a common subclonal origin. *Why were these percentages so low? If the seed and soil theory of metastasis were correct, the percentages should exceed 80–90%.*

These heterogeneities cannot be explained by free cancer cells, free circulating DNA, or somatic mutations, or by applying an anatomical mechanistic vascular (lymphatic and hematogenous) approach, which nonetheless remains widely taught in oncology training programs. Training suggesting that anatomy facilitates cancer cell spread through "highways" does not provide a sufficient explanation. A more nuanced view of the cancer microenvironment would aid in understanding the roles of signaling and crosstalk necessary for cell migration and subsequent increases in motility.

Cancer microenvironment

The heterogeneous cancer microenvironment, including cell compartments, signaling, and cancer spread, together with transformation of the pre-cancerous niche (PCN) to the premetastatic niche (PMN) and increased cell mobility can explain the heterogeneous clinical findings.

In gastric cancer cells, CAFs maintain the chronic inflammation stage, with ongoing activation of the PCN, by increasing p300, which in turn activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling, thus resulting in mesenchymal stem cell (MSC) differentiation into CAFs [**52**]. This self-driven, persistent inflammatory stimulation has also been observed in breast cancer cells [**53**]. Fibroblasts and CAFs are prominent in the cancer microenvironment. Essential information regarding heterogeneity is provided in the supplement (Supplement, part 6, Fibroblast heterogeneity).

Fibroblasts themselves show high heterogeneity and are known to convert to CAFs and to promote metastasis in cancers of the breast [**54**], prostate [**55**], pancreas [**56**], and colon [**57**]. Co-cultivation of cancer cells with fibroblasts increases the transformation of fibroblasts into CAFs [**58**].

Do fibroblasts derive from EMT during the chronic stress escape strategy (CSES)? Or do fibroblasts derive from the remodeled tumor microenvironment during carcinogenesis through the PCN sequence or perhaps from a normal cell to cancer cell transition (NCCCT) sequence? These questions prompt additional questions: are migrating cells the source of metastasis in distant organs, or do these secondary cancers intrinsically arise from the organ where the metastasis is found?

The fibroblast atlas cannot explain the spatial dynamics of fibroblasts, nor can it clarify the locations from which each fibroblast derives, although it advances knowledge regarding heterogeneity and orthologs in different species. Intriguingly, gene expression studies [**59**] have related the heat maps of the relative average expression of the most strongly enriched genes for each cluster to particular organs, such as Ccl19, Ccl21a, and Bst1 in lymph nodes; Cxcl12, Lepr, and Sp7 in bone tissue; Npnt and Ces1d in alveolar lung tissue versus Hhip and Aspn in peribronchial lung tissue; and Fbln1and Sfrp1 in intestinal tissue. However, none of these location-specific gene expression findings answer the key question of how these relate to metastasis.

Next to fibroblasts and fibrocytes, transition to CAFs can occur in mesenchymal stem cells (MSCs) [**60**], hematopoietic stem cells [**61**], and adipose-derived MSCs [**62**]. The transition from MSCs is dependent on myeloid zinc finger 1 (MZF1) and transforming growth factor β (TGFβ), which are mediated by osteopontin (OPN) [**63**]. OPN is an acidic hydrophilic glycophosphoprotein that influences αvB3-integrin and CD44 and serves as a cell attachment protein. The c-Jun homodimer of AP-1 is necessary for OPN promoter activity and binds the OPN promoter in 4T1 cells; its levels are increased by PI3K-dependent JNK- and c-Jun activation, thus promoting metastatic behavior, such as adhesion, migration, and invasion *in vitro* [**64**].

To increase cancer drug efficiency, CAF research has focused on overcoming anticancer drug resistance [**65–68**] and promoting understanding of the CAF signature to evaluate immunotherapy responses [**69**].

Furthermore, MSCs can be recruited from the bone marrow, transform into fibroblasts, and subsequently transition into CAFs [**70**]. A pH decrease within tissue can result in the transitioning of MSCs to CAFs [**71**].

CAFs show neuroendocrine differentiation in a CD105-dependent manner [**72**]. This neuroendocrine differentiation has been associated with circulating tissue inhibitor of metalloproteinase-1 (TIMP-1) in a manner dependent on ERK and NF-κB in metastatic castration-resistant prostate cancer [**73**]. *These findings support the theory that the primary sources of epithelial cancers are fibroblasts and CAFs and not epithelial cells* [**15**].

To shed light on the heterogeneity of fibroblasts and CAFs, studies have conducted single-cell RNA sequencing in pancreatic cancer tissues from six human patients and adjacent normal pancreatic tissue from two of these patients, as well as from Kras+/LSL-G12D; Trp53+/LSL-R172H; Pdx1-Cre (KPC) pancreatic cancer in mice [**74** and Supplement, part 4]. Studies focusing on p53 downstream of CAFs [**75–77**] have suggested that CAF heterogeneity is associated with Yes protein 1 (YAP1), as indicated by the activation of MSCs [**78**], in cancers of the breast [**79**], pancreas [**80**], prostate [**81**], and colorectum [**82**].

Furthermore, disruption of homeostatic signaling in Dickkopf-3 (DKK3), an effector of heat-shock factor 1 (HSF1), induces the transcriptional co-factors YAP (gene Yap1) and TAZ (gene Wwtr1) via Wnt signaling, which is crucial for the tumor-promoting ability of CAFs [**83**]. The complexity of YAP1 homeostasis is indicated by the influence of cytoskeletal dynamics, because myocardin-associated transcription factors are required for the YAP pathway for CAF contractility and for its proinvasive properties [**84**].

Extracellular matrix (ECM) stiffness induces the activity of Rho-associated coiled-Coil kinase (ROCK), integrin clustering, mitogen-activated protein kinase 1 (MAPK 1, extracellular signal-regulated kinase 2, ERK2) signaling, and subsequent nuclear accumulation of SNAIL1, which in turn interacts with YAP1 [**19, 85**].

A more detailed signaling and crosstalk information about YAP, and fatty acid desaturase 2 (FADS2, ω-6-desaturase, D6D) signaling in the disruption of signaling homeostasis induced

crosstalk in the carcinogenesis paradigm "Epistemology of the origin of cancer" can be found elsewhere (*Please see figures 1 to 3 in* [**19**]). More detailed information on the associations between CAF interactions and Neuropilin-1 (NRP1) is provided in the supplemental material (Supplement, part 7, CAF interaction with Neuropilin-1 and EGF-like domain-containing protein 7).

The copper-dependent enzyme lysyl oxidase (LOX) [**14, 15, 86–88**] is activated by fibroblasts under stress [**89**], crosslinks collagen [**90**], and promotes cancer *in vivo* [**91**]. Moreover, if the remodeled matrix persists in the lamina fibroreticularis, a PCN with enhanced stiffness and cell transition properties is generated [**14–19**].

H. pylori induces NF-κB and the YAP1 axis in gastric pre-cancerous *Helicobacter*-induced lesions [**92**] and increases SALL4, which induces the CAF phenotype [**93, 94**]. *H. pylori* infection promotes hepatoma-derived growth factor (HDGF) expression in human gastric cancer. Subsequently, HDGF recruits MSCs and regulates their differentiation into myofibroblast-like cells expressing α-smooth muscle actin (α-SMA), procollagen α1, tropomyosin I, desmin, fibroblast activation protein (FAP), and fibroblast markers prolyl-4-hydroxylase A1 (PHA1) and fibroblast specific protein-1 (FSP-1)/S100A4 [**95**].

More detailed information on the association of Sal-like protein 4 (SALL4) and miR-33 is provided in the supplemental material (Supplement, part 8, Sal-like protein 4 and miR-33).

CAFs can also derive from epithelial cells, pericytes, adipocytes, and endothelial cells [**96, 97**]. Furthermore, inhibition of the histone methyltransferase enzyme euchromatic histone-lysine N-methyltransferase 2 (EHMT2, G9a) decreases active CAFs to a less proliferative/invasive state [**98**].

In vitro, macrophages (THP-1 cells) induce differentiation to the CAF phenotype, which can lead to gastric epithelial lesions with malignant features via EMT [**99**]. Again, these findings indicate that *the primary sources of epithelial cancers are fibroblasts and CAFs, but not epithelial cells* [**15**]. The tumor microenvironment provides the prerequisites for cell migration from the primary tumor to distant sites (metastasis).

Cell migration

Cell migration is a complex and poorly understood process with central roles in embryogenesis, physiology, and the pathophysiology of diseases [**100**]. The following statement by Erwin Büning (1906–1990), who discovered the internal clock together with Jürgen Walther Ludwig Aschoff (1913–1998) and Colin Stephenson Pittendrigh (1918–1996), remains relevant: "*Perhaps even today we do not fully realize the inherent complexity of many biological phenomena*" [**101**].

The dynamic combination of local and peripheral conditions, cell-cell cell-microenvironment communication and adhesion results in signaling and crosstalk, wherein the information processing is akin to changes in language and grammar with modifications of polarity alignment and direct locomotion and velocity. The cellular microenvironment with its modifications of stiffness and elasticity by crosslinking changes, not just cell communication locally, but also within the cell network, its organization (tissue). Together, these factors can result in cell transition with malignant consequences for the local microenvironment, an organ, or the whole organism, thereby resulting in metastasis.

Additionally, a difference exists between single cells or compartments and multiple cells, such as cancer satellites that move and travel alone or together. According to a simulation analysis, whether cells join in small or large numbers during cell movement appears irrelevant, because cell polarity determines cell orientation and the direction of migration [**102**].

Stiffness gradient

A rigid matrix promotes cell proliferation [**103**] through a process called mechanotransduction [**104, 105**], which is dependent on modulation of integrin expression [**106, 107**]. Independently of cell size or cell division, cell migration typically aligns along with the stiffness gradient [**108**].

Other variables influencing cell migration, beyond the composition of the cytoskeleton and cytoplasm [**109**], include ion channels [**110**], various types of signaling [**111**], and chemotaxis [**112**].

Chemotaxis

Chemotaxis, locomotion along a gradient [**101**], was observed and reported in bacteria by Theodor Wilhelm Engelmann (1843–1909) in 1881 [**113**] and by Wilhelm Friedrich Philipp Pfeffer (1845–1920) in 1884 [**114**]. A statement by Pfeffer, in 1893, that "*the senses of unicellulars are not poorer than those of vertebrates*" [**101**], was considered sacrilegious at the time. Changes in chemotaxis always impair cell motility [**115**].

However, polarity and lamellipodia are also important for cell mobility, thereby enabling pre-cancerous and cancer cells to cross the basement membranes, enter the circulation, and become dispersed.

Cells use modifications of plasticity and actin-rich protrusions (filopodia, lamellipodia, invadopodia, podosomes, and lamellipodia) to migrate through the extracellular matrix (ECM), access the endothelium, and consequently undergo transendothelial migration and entry into the vascular system [**116**].

Spatial asymmetry and polarization

Spatial asymmetry causes morphological polarization with front and rear differentiation, thus defining the direction of cell migration. This polarization can occur in both individual and collective cell migration on the basis of changes in orientation and composition of filamentous F-actin distribution [**100, 117**]. However, over a distance of several cell lengths (~100 μm), no cell always follows a constant path in space [**118**]. Contractile myosin components are preferentially localized at the rear of the cell, whereas actin is localized in the front [**119**]. Turning cells have asymmetric shapes and actin distributions. Myosin contractions at the rear of the cell use functions similar to rear-wheel steering in a car to remain stable during sustained rotation.

Human bladder epithelial cancer cells are more deformable than normal cells [**120**]. This finding has also been observed in breast cancer, in which an approximately ~50% decrease in filamentous actin (F-actin) during cytoskeletal reorganization has been associated with increased metastatic potential [**121, 122**]. The loss of polarity in cancer tissue was reported in 1941 in carcinoma in situ (CIS) [**123**], which was first described in 1932 as a *noninvasive carcinoma* of the breast [**124**]. Broders described CIS in the epithelial layer as a lesion of malignant epithelial cells, with their progeny located at or near positions previously occupied by their ancestors before malignant transformation or migration and breaching of the basement membrane. However, noninvasive means non-migrating, in concordance with actin findings. CIS does not show lymph node or other metastasis, but CIS in the periphery with multifocal or multicentric localization is present in as many as 40% of breast cancers [**125, 126**]. More detailed information regarding CIS is provided in the supplemental material (Supplement, part 9, Carcinoma in situ).

Migration induced by signaling

The anti-inflammatory lipid mediator Resolvin D1 (RvD1) [**127**], within a co-culture of CAFs isolated from hepatocellular carcinoma (HCC), has been found to suppress cartilage oligomeric matrix protein (COMP) secretion, thereby inhibiting CAF-induced EMT [**128**]. Plasminogen activator inhibitor-1 (PAI1) from CAFs in esophageal squamous cell carcinoma (ESCC) binds the PAI-1 receptor low-density lipoprotein receptor-related protein 1 (LRP1), thereby activating Akt and Erk1/2 signaling, and inducing migration and invasion of ESCC and macrophages [**129**].

CAF-inducing migrating phenotype

CAFs increase the expression of alpha smooth muscle actin (α-SMA), fibroblast activation protein (FAP), fibroblast-specific protein 1 (FSP1), platelet-derived growth factor receptor (PDGFR)-α/β, and vimentin [**130**]. These increases are associated with cell contractility (α-SMA), FAP, cell differentiation (FSP-1, S100A4), receptor tyrosine kinase activity (PDGFR-α/β), and cell motility (vimentin). Coexpression of vimentin and keratin intermediate filaments in cancer cells enhances the migratory and invasive subtype [**131–133**].

FSP-1 binds $Ca2^{+}$ and is expressed by inflammatory macrophages [**134**], thus explaining the close interaction of cancer cell migration with parts of the immune system. Changes in transcription factor expression contribute to the disruption of homeostasis and consequent transformation to heterogeneous CAFs [**135**]. This heterogeneity has been reported to be associated with the provenance of CAFs [**136**].

Furthermore, the heterogeneity suggests that [**137**] CAR-T cell technology is unlikely to be helpful in the short or mid-term for heterogeneous cancers. In contrast, if, for example, leukemia were caused by one heritable mutation, the CAR-T approach would be reasonable.

Highly aggressive hepatocellular carcinoma (HCC) cell lines with high metastatic potential promote liver fibroblast migration and transformation into CAFs [**138**]. The mechanism involves the EGF-like domain multiple 7 (Egfl7). Early HCC recurrence (within 2 years) exhibits greater CAF infiltration than observed in patients without early recurrence, thus indicating an important role of CAFs. More detailed information on the association of CAFs with Egfl7 is provided in the supplemental material (Supplement, part 7, CAF interaction with Neuropilin-1 and EGF-like domain-containing protein 7).

Changes in the stiffness gradient, chemotaxis, spatial asymmetry, and polarization induce enhanced cell migration and immune system suppression, thereby increasing cell motility and cell mobility, and enabling metastasis.

Cell mobility

Decreased cell-cell interactions result in changes in epithelial morphology, cell transition, and cell movement [**3, 139, 140**]. Downregulation of Ca^{2+}-dependent homophilic adhesion receptors and cadherins, such as E-cadherin, during carcinogenesis is associated with increases in mesenchymal markers, such as fibronectin, and vimentin. As E-cadherin decreases, greater cell motility and higher rates of cell transformation are observed [**141**]. This response appears to be a last attempt by the biological system to restore homeostasis.

The actin protein Espin is overexpressed in cancer and promotes filopodial formation, thereby facilitating cancer cell migration and metastasis [**142**]. The microfilamentous cytoskeleton turnover in polymorphonuclear neutrophils is activated by chemotactic factors [**143**]. Exposure to the carcinogen, 7, 12-dimethylbenz [a]anthracene (DMBA), induces premalignant lesions in hamster cheek pouch mucosa, and is followed by formation of pseudopodia in stromal tissue cells and epithelia, including surrounding leukocytes [**144**].

Joseph Locker, in 1970, demonstrated that 48 hours after liver cancer cell inoculation in chick embryos, the tissue was invaded, and pseudopodia were observed together with loss of tight junctions, disruption of the epithelial organization, and liver metastases after 72 hours [**145**].

Lamellipodial formation

Lamellipodial formation is a complex actin-dependent process that results in the formation of flat sheet-like protrusions, thus leading to slow adhesive movement [**146**]. Lamellipodia preferentially extend in the direction of gradients [**147**]. Elongation of connective tissue *in vivo* and *ex vivo* results in the formation of new lamellipodia in fibroblasts within minutes, whereas in unstretched tissue, the fibroblasts show normal dendritic morphology [**148, 149**]. Although movement is generally slow, changes in the composition of actin filaments within lamellipodia occur rapidly with polymerization and depolymerization [**150**]. However, for cell migration, another precondition beyond the deformation of the cytoplasm must be met. Deformation and expansion of the laminar surface of the nucleus are required to enable cell migration through narrow spaces [**151**], such as the stiff ECM.

Furthermore, transformation of MSCs into CAFs has been described [**152**]. Ongoing TGFβ elevation (chronic inflammation) results in CAF elongation mediated via Rac, RhoA, and ROCK, and leads to cell spreading, lamellipodial formation, and spheroid invasion [**153**].

Cancer cells, as well as the PCN, induce LOX activity, and increased focal adhesion kinase (FAK), src, and Crc [**154**]. CAFs induce p130(cas), thus resulting in the formation of p130(cas)/crk/DOCK180 and, via RAC-GTP, increased lamellipodia, decreased actin fiber function, and elevated cell motility and mobility (*see below* **FIGURE 2**). No rapid movement is necessary, because the initial barrier after the first cancer cell has developed and integrated into the target tissue is loss of adhesiveness mediated by a decrease in E-cadherin [**3, 14**].

Crossing the basement membrane

When epithelial cancer cells grow, the basement membrane, including collagen type IV, poses a barrier to cell movement or a so-called restriction line. Alpha 3 beta 1 integrin [**155**] and metalloproteinase 9 (MMP-9 or gelatinase B) [**156**] are associated with increased collagen IV degradation, invasiveness, and migration [**157**], thus facilitating the transport of cancer cells across the basement membrane [**158**].

Extracellular vesicles

Long distance cell communication influences metastasis in a different manner. Cells can release extracellular vesicles (EVs), which are nanoparticles 50–500 nm in diameter [**159**]. Despite having been known for approximately 30 years, EVs were initially assumed to be cellular "junk" [**160**]. EVs are secreted vesicles, including exosomes and microvesicles, that contain proteins, lipids, and nucleic acids (such as mRNA and miRNA). In 1981, EVs were recognized as vesicles containing enzymes [**161**]. Later, EVs were found to be able to communicate over long distances [**162**].

Furthermore, EVs can modulate the immune system around primary tumors, thus creating pro-metastatic conditions. This phase, in accordance with seed and soil theory, is described as "preparing the soil" [**163**]. Autocrine, paracrine, and endocrine signaling induced by EVs does not require direct cell-to-cell contact [**160**]. EVs can contain the small GTPase Rab27a, which is overexpressed in breast cancer [**164**]. Inhibition of Rab27a in breast cancer decreases EV secretion, the number and size of lung metastases [**165**], and the accumulation of tumor-promoting tumor-associated neutrophils (TANs) [**160**]. EVs

easily travel through the ECM. Aquaporin-1 (AQP1) within the EV membrane mediates EV deformability [159] and therefore facilitate easy and efficient EV travel through the ECM to target cells. Plant-derived EVs might provide a novel tumor-targeting delivery system for cancer treatment [**166**].

Blebbing (motility without adhesion)

Blebs are short-lived cell membrane protrusions which are bulky and have a rounded morphology [**167**]. Blebs undergo rapid expansion followed by a short static phase and slow retraction lasting approximately 1 minute [**168–170**]. Blebs were first observed as transient changes in corneal endothelium by doctoral student Steve Zantos and his supervisor Brien Anthony Holden (1942–2015) [**171**]. After lens insertion, blebs can be seen for approximately 10 minutes. The expansion time with intracellular pressure on the cytosol initiates bleb formation and is estimated to be approximately 5–30 s [**172**]. Polarized bleb accumulation can persist for at least an hour and is integrin dependent [**173**]. Signaling by FAK, integrin α2, and junctional adhesion molecule-1 (JAM-1) is involved in blebbing [**174**].

Blebs alter cell movement in vitro and in vivo, thus enabling amoeboid-like cell motility [**175**] without adhesion [**176**]. Early blebs are initially actin negative but later become actin positive, and the hydrostatic pressure necessary for movement relies on non-muscle myosin II (NMII) contractility [**172**]. Blebs are associated with decreases in lamellipodia [**172, 177**]. If the proportion of blebs becomes disproportional, the cell's locomotion markedly slows and the movement becomes less directed.

Furthermore, blebbing promotes cancer invasion, migration, and metastasis [**170, 173, 174, 179, 180**]. Increased blebbing is associated with aggressiveness and metastatic behavior [**173**]. Changing the ratio of lamellipodia to blebs also influences the straightness of movement. The locomotion strategy of progenitor cells in tissue appears to involve a combination of blebbing and rapid straight-line forward movement. Lamellipodia are believed to be necessary for fast movement, whereas blebs are believed to be required for tumbling movements. The combination of both is believed to provide an optimized strategy for the precise movement of cancer cells.

Switching cancer cell motility

*Established liver tumors recruit CAFs and stimulate their own growth [***181, 182***]. Cancer cells can be cohesive or mobile. TGFβ signaling, together with Smad4, EGFR, Nedd9, M-RIP, FARP, and RhoC, can collectively alter the motility of single or multiple cancer cells [***183***]. In contrast to primary cancers, lymph node metastases intriguingly involve a collection of initially non-motile cancer cells.*

CAFs suppress the immune system

High SMAD3, even independently of TGFβ, recruits CAFs in lung adenocarcinoma, and CAFs in turn increase matrix metalloproteinases (MMPs) [**184**] and downregulate MHC class I-restricted T-cells (CD8+ T-cells), which can kill cancer cells [**185**]. CD4+ T-helper (TReg) cells are increased by CAFs [**186**], whereas CCL2 increases macrophage suppression [**187**]. Furthermore, CAFs regulate the immune system [**188, 189**] and can act as MHC class II-expressing CAFs presenting antigens to CD4+ T cells, thereby modulating the immune response in pancreatic tumors [**74**]. However, the disruption of homeostasis by CAFs can also suppress the immune system and facilitate pro-cancerous growth [**190**]. More information regarding the important interactions of CAFs with Transgelin-2 and cluster of differentiation 74 (CD74) is provided in the supplemental material (Supplement, part 10, CAF, Transgelin-2, and cluster of differentiation 74).

The cancer microenvironment consists of tumor-associated cells (TACs), which further influence cell migration and mobility, and create the preconditions for metastasis—the actual process of cancer cell spread, which is followed by traveling ('circulation') and extravasation.

Tumor-associated cells

TACs are found in the tumor center and in its vicinity. These cells include tumor-associated macrophages (TAMs), tumor-associated platelets (TAPs), tumor-associated neutrophils (TANs), tumor-associated lymphocytes, tumor-infiltrating lymphocytes, and tumor-associated dendritic cells (myeloid-derived suppressor cells). In principle, most TACs are found in cancers with a pro- or anti-cancer role, and each type can be heterogeneous.

Tumor-associated macrophages and M2 macrophages

TAMs are broadly classified into anti-tumor M1 macrophages (classically activated M1 macrophages) and cancer-inducing M2 macrophages (alternatively activated M2 macrophages). These macrophages are associated with cancers of the breast [**191–193**], stomach [**194**], and liver [**195**]; cholangiocellular carcinoma (CCC) [**196**]; HCC [**197**]; and prostate carcinoma [**198–200**]. TAMs can derive from so-called cancer stem cells [**201**].

M1 macrophages are classically activated in response to interferon-gamma (IFN-γ) and lipopolysaccharide (LPS), and are anti-tumorigenic. They are characterized by TNF-α, IL-1β, IL-6, nitric oxide synthase (iNOS), and reactive oxygen species. They express CD80 (B7–1), CD32, CD68, and CD11b (integrin alpha M or ITGAM), and they are crucial for immunity by eliminating pathogens and cancer cells [**202–208**].

M2 macrophages are activated by IL-4, IL-10, and IL-13, and express various receptors, such as TGFβ, CCR2, CD163, CD206 (mannose receptor), CXCR1, CXCR2, Dectin-1, scavenger receptors A (CD204) and B-1 (SR-B1), macrophage receptor with collagenous structure (MARCO, SR-A6), and arginase 1 (ARG1). These findings might explain why a TH2-type immune response is observed in schistosomes, which causes bladder cancer [**209**]. More information regarding the interactions of Alpha-1-B glycoprotein (A1BG) is provided in the supplemental material (Supplement, part 11, Alpha-1-B glycoprotein).

When stimulated by cytokines, macrophage polarization and transition can change from M1 to M2, and vice versa. Subsets of M2 macrophages include M2a, M2b, M2c, and M2d. Cancer cells expressing cluster of differentiation 47 (CD47) induce further immunosuppression by inhibiting phagocytosis and promoting cell migration [**210**]. More information regarding the different M0 expression profiles, as well as CD47 expressing cancer cells suppressing phagocytosis is provided in the supplemental material (Supplement, part 12, TAM profiles and cluster of differentiation 47).

Tumor-associated platelets

TAPs have a more complex role in nature and therefore are not differentiated by type 1 or 2. Pro-tumorigenic TAPs protect cancer cells against immune attack; mediate adhesion, extravasation, and angiogenesis. They also induce cell transition or the release of soluble platelet growth factors. Anti-tumorigenic TAPs increase macrophage recruitment and, after activation, can destroy cancer cells [**211, 212**]. More information on platelets and TAPs is provided in the supplemental material (Supplement, part 13, Thrombocytes).

Thrombocytosis (high platelet count) and/or megakaryocytosis is associated with cancers and poor survival in epithelial cancers [*reviewed in* **213**], whereas inhibiting platelets decreases metastasis [**214**]. Furthermore, cancer cells activate and form aggregates with platelets and leukocytes and consequently are able to evade the immune system [**215, 216**].

Platelets themselves are activated by multiple pathways, such as neutrophil-released cathepsin G [**217**], thromboxane A2 (TXA2) [**218, 219**], high-mobility group box 1 (HMGB1)/ Toll-like receptor 4 (TLR4) axis, and adhesion G protein-coupled receptor (GPCR) cluster of differentiation 97 (CD97). Platelets support lung microvascular integrity independently of their classic hemostatic pathways [**220–222**]. Platelets contain factors that promote cell survival and support the endothelial barrier [**223, 224**], and influence the programmed cell death pathway [**225–227**]. Moreover, platelets are present not only in the vascular space during lung inflammation but also actively enter the alveolar space during experimental lung injury [**228, 229**].

Although platelets play major roles in cancer metastasis by facilitating tumor cell survival, immune evasion, and cancer spread to distant sites, one aspect and role in metastasis might not have been interpreted correctly.

Aspirin has anti-platelet effects that correlate with favorable prognosis and diminished clinically observed metastases [**127, 230**]. These observations might explain experimental data from the 1980s on the anti-COX effects of aspirin, which indicated negative findings [**231**]. The anti-platelet aggregation effects of aspirin were ignored. Chemotherapy suppresses platelet production in the bone marrow, and this cytotoxic effect alone might explain why the role of platelets in epithelial cancer metastasis were underestimated.

Platelets bind lysophosphatidic acid in breast cancer [**232–234**], ovarian cancer [**235, 236**], prostate cancer [**237**], kidney cancer [**238**], and oral squamous cell carcinoma [**239**]. Subsequently, they stimulate osteoclast resorption through IL6 and IL8, thus resulting in bone metastasis [**240**] and osteosarcoma progression [**241**].

For metastasis, complement activation and thrombin [**242**] are also necessary. Thrombin increases metastasis [**243**] and activates proteinase-activated receptor 1 (PAR1), a receptor highly expressed on platelets and endothelial cells [**244**]. In contrast, the inhibitor hirudin decreases metastasis [**245**]. Thrombospondin-1 (TSP-1) and prosaposin (PSAP) have diverse functions. More detailed information regarding TSP-1 and PSAP is provided in the supplemental material (Supplement, part 14, Thrombocytosis, Thrombospondin-1).

Metastatic spread is highly heterogeneous, but spleen metastasis is notably very rare. The spleen is distinct from other organs in that it filters platelets highly effectively, thus suggesting that platelets play a critical role in metastasis. Furthermore, the liver is involved, and metastasis occurs far more often to the liver than any other organ. An important factor, sialic acid, must also be considered as further discussed.

Platelet clearance

Platelets have a lifespan of approximately 10 days. Platelet clearance occurs within the spleen by splenic macrophages. Additionally, aging platelets are eliminated in the liver by Kupffer cells, probably through desialylation, a process in which sialic acid on the cell surface is removed from glycans, glycoproteins, or glycolipids [**246–248**]. Asialoglycoprotein receptor 1 (ASGR1), a sialic acid receptor, participates in clearance of sialic acid from the liver and thereby functions as a tumor suppressor. This receptor is often downregulated in HCC versus normal liver tissue and is associated with a poor prognosis.

ASGR1 knockout promotes HCC development [**249, 250**]. In contrast, asialoglycoprotein receptor 2 (ASGR2) acts as a tumor promoter in gastric cancer [**251**] and is associated with cancer recurrence [**252**]. Moreover, high expression of ASGR2 is associated with gastric lymph node metastasis and venous invasion [**253**]. More detailed information regarding desialylation and platelet clearance is provided in the supplemental material (Supplement, part 15, Desialylation and thrombocyte clearance).

Blood transfusion activates TAPs

Controversial positive and negative prognostic studies have described outcomes after blood transfusion in patients with cancer [**254**]. However, red blood cell transfusion results in cancer cell activation and aggregation by the adenosine diphosphate (ADP)-P2Y12 receptor pathway [**255**]. Furthermore, red blood cell transfusion is associated with decreased survival, earlier recurrence, and increased metastasis [**256–260**]. Furthermore, patients with early stage I breast cancer patients who receive blood transfusions have poorer survival and earlier recurrence than patients without transfusion post-surgery [**261**].

The associations found in patients with cancer after blood transfusion (decreased survival and disease-free time, higher metastasis rates) are logical, particularly in the context of TACs, because transfusion-induced activation of TACs, particularly by TAPs, might explain these observations.

Tumor-associated neutrophils

TANs have various subtypes: N1 has anti-tumoral roles, whereas N2 facilitates migration of cancer cells [**262, 263**]. In CRC, IL-8 promotes neutrophil activation [**264**], and TAN promotes peritoneal cancer cell adhesion [**265**]. N1-TAN releases hydrolytic enzymes, or activates macrophages, dendritic cells, or T-cells. N2-TAN induces gelatinase B, an important enzyme for cancer growth and metastasis [**266**]. TANs release TIMP-free MMP-9, which is associated with very aggressive cancer [**267**].

Moreover, CRCs induce polarization between N1 and N2 by TGFβ with consequent increase in the N2 subtype [**262, 268**].

N2 recruitment occurs via CXCR2 in a manner regulated by IFN-γ [**269**]. Precursors of TAMs and TANs are located in the spleen and are readily recruited [**270**]. TANs promote invasion of cancer cells into lymph nodes [**271**].

Circulating TANs suppress peripheral leukocyte activation [**272**], and CTCs protect themselves via CD44 building clusters [**273**]. Cathepsin C released by neutrophils is associated with cancer progression and metastasis [**274**], and is also correlated with M2 macrophages in lung cancer [**275**]. The inhibition of TAPs diminishes this effect and decreases metastasis [**276**].

Cancer cells, as well as CAFs, induce the formation of neutrophil extracellular traps (NETs), which promote migration and metastasis. NETs are found in various epithelial cancer tissues, the vascular system, and in distant metastases. An anti-NET approach might inhibit both migration and metastasis [**277–279**].

Abundant polymorphonuclear myeloid-derived suppressor cells in primary and metastatic lung cancer have been measured in the blood and found to be inversely correlated with low frequencies of NK cells [**280**]. Furthermore, NETs promote liver metastasis and have been measured in patients undergoing curative liver resection for metastatic CRC [**281**]. NETs can trap CTCs [**282**] and serve as an adhesion substrate [**283**]. TANs appear to facilitate omental metastasis in ovarian cancer [**284**]. NETs promote liver micro-metastasis and have been measured in pancreatic cancer through the activation of CAFs [**285**]. NETs from TANs wrap around and consequently protect CTCs against immune attack [**286**]. In addition, inhibition of NETs protects against adhesion to liver sinusoids and metastasis [**287**].

Furthermore, TAPs, via αIIbβ3, shield CTCs in the bloodstream and consequently protect them against immune attack [**288**]. TAN attachment, via ICAM-1 and Mac-1, to CTCs enables transendothelial migration and extravasation [**289**]. Neutrophil-derived leukotrienes facilitate colonization of distant tissues [**290**]. Furthermore, TANs form clusters in the bloodstream [**291**].

Each tumor-associated cell (TAC) type has anti- and pro-tumor functions. As cancer growth increases, pro-tumor functions increase, and immuno-competent cells are suppressed

(immune escape). Therefore, pro-tumor TACs promote cancer cell dissemination from primary tumors, as well as transendothelial migration, vascular stream survival, nidation, colonization, and metastatic growth at distant sites.

Chemokine CXCL12 (stromal cell-derived factor 1, SDF-1) signaling

CAFs produce the chemokine CXCL12 (stromal cell-derived factor 1, SDF-1), which is chemotactic for mesenchymal cells [**292**]. Furthermore, fibroblasts [**293**], bone marrow fibroblasts [**294**], CAFs [**295**], and particularly platelets are major sources of CXCL12 [**296, 297**]. Information regarding butyrophilin signaling and crosstalk in this context is provided in the supplemental material (Supplement, part 16, Butyrophilin molecules).

CAFs coat cancer cells, thereby suppressing T-cell infiltration by CXCL12 and resulting in quiescence of the cancer-immune response, with expression of Cxcl9 [**298**].

The maintenance of homeostasis includes diverse responses across all biological systems. Therefore, the disruption of homeostasis in cancer is both complex and heterogeneous. The CAF subtype can switch from an immune-suppressive (CXCL12+/CXCL9–) to an immune-activating (CXCL12–/CXCL9+) subtype. Furthermore, chronic inflammation increases CXCL12 [**299**] which in turn induces cancer progression through AKT and ERK signaling [**300–302**].

Cancer cells proliferate through PI3k/Akt signaling by CXCL12 [**303–306**]. Increased TGFβ signaling induces EMT via Wnt in breast cancer [**307**] and, TGFβ, together with CXCL12 expression, promotes cervical and breast cancer growth [**308**]. Furthermore, cancer cells follow a CXCL12 gradient [**309**]. More detailed information on CXCL12 is provided in the supplemental material (Supplement, part 17, Chemokine CXCL12).

Egfl7 increases FAK and Akt phosphorylation via the αvβ3 integrin receptor, and both recruit and activate liver fibroblasts to adopt the CAF phenotype [**138**]. For example, integrin α6β4 induces formation of lamellae and cell migration [**310**], with upregulation of PI3K and NF-κB [**18**]. Furthermore, integrin activation results in the production of fibronectin and insoluble fibrils, decreased p38 and cell proliferation [**311**]; consequently, cell binding promotes migration [**312**].

Cancer cell coating by CXCL12-Keratin 19

Cancer cells can be coated through CXCL12–Keratin-19 filamentous formation and consequently hidden from T cell–mediated immune reactions [**313**]. Subsequently, intravasation, traveling ('circulation'), extravasation, and colonization of distant organs increase. Cancer cells can assemble CXCL12 together with Keratin 19 as a coating for immune evasion. Further details are discussed below.

Keratin 19 [**314**] is part of the cytoskeleton in epithelial cells and is found in epithelial cancer cells [**315, 316**]. CXCL12, a small cytokine, was identified in 1993 from a bone marrow stromal cell line and described as an intercrine-macrophage inflammatory protein [**317**]. Its structure was identified in 1994 [**318**]. While the CXCL12 mRNA is decreased [**319**], its expression in tissues is associated with metastasis.

The interplay of chemokines with the receptor as CXCL12/SDF-1alpha and CCL21/6Ckine exhibit peak levels of expression in organs that are the first destinations of breast cancer metastases [**309**].

The underlying complex framework described herein provides a basis for understanding metastasis in a new light. Several terms used herein are defined below.

Niche

The term niche comes from the Latin nidus, meaning nest. Pre-metastatic niches are a set of prerequisite conditions for tumor growth and access to the vascular system (intravasation: hematogeneous and lymphatic). Pre-metastatic niches are followed by circulation (better: traveling). Only after nidation can colonization occur at sites distant from the primary cancer, thus resulting in metastasis. To date, the term "metastatic niche" has been characterized as a region of increasing metastatic potential [**320**], followed by perivascular conditions [**321**]. In the bone marrow, the metastatic niche takes the form of an endosteal niche in regard to osteoblasts [**322**].

Cancer satellite (CS)

The definition of cancer satellites provided by the National Cancer Institute is "discrete tumor cell clusters near the primary tumor." However, the original meaning of satellite comes from the Latin satelles, meaning one who escorts or follows e.g. behind an important person. We therefore use the term "satellite" to describe cancer satellite complexes in metastasis in the original (non-modified) manner, as a cell or particle escorting another from one location to another more distant location.

Circulation

The term circulation is not completely correct, because it incorrectly implies that cancer satellites can circulate within the human body for more than one round of circulation. Only one cancer cell is found per million cells [**323, 324** *reviewed in* **325**]. Only 0.2% of cancer cells in circulation form metastases, whereas 99.8% are effectively eliminated by the immune system. The term "circulation" in the context of cancer cells and metastasis is simply an incorrect assumption. However, to avoid confusion, we use this term because it has become commonplace, together with the much more appropriate, correct term of "traveling".

Gradient

A gradient in cell biology, and within the extracellular matrix, is a fundamental process, enabling embryogenesis, as well as adapting conditions (compensate) disruption of homeostasis. A gradient is a measure of the spatial variations over a certain space in the composition (secretion by cells of types and amount of protein and/or enzymatic modification), mechanics (change of mechanical forces by properties in stiffness and elasticity) and chemistry (changes in the concentration), resulting into a physical quantity. By this, the gradient by component, mechanical, chemical and physical composition, guide movements, such as cell migration towards a direction.

Adhesion

Adhesion is fundamental to cell-cell communication and crosstalk [**3, 14**]. Adhesion after ECM migration and invasion precedes transendothelial migration and is mediated by the carbohydrate-binding molecules known as selectins [**326–328**]. The three main types of selectins are E-selectin (expressed on activated endothelial cells and promyeloblast cells), P-selectin (expressed on endothelial cells and platelets), and L-selectin (expressed on activated platelets and leukocytes). To plausibly explain how metastasis occurs, pre-conditions for cell spread in terms of adhesion, E-selectin, P-selectin, and L-selectin are important, and are detailed in the supplemental material (Supplement, part 19, E-, P-, and L-selectin). Transendothelial migration is multifaceted and has been reported in detail elsewhere [**100, 102, 108, 110, 116, 119, 176, 294, 303**].

Metastasis

In cancer, metastases describe secondary cancers that occur at distant sites in the body from primary cancers. We recognize that 10^7 cells (i.e., 10 million or 10, 000, 000 cells) must be present for a tumor nodule to be detected by imaging, and the average number of cells in a tumor when it is first palpable is 10^8 cells (i.e., 100 million or 100, 000, 000 cells) [**19**].

Therefore, how carcinogenesis and its first cancer cell occurs must be identified. Such identification has been systematically performed over 25 years [**3, 4, 14–19, 127**]. The same methods have also been applied to metastasis, to identify the essential sine qua non prejudices and to elucidate what comes first and later results in transendothelial migration, intravasation, and traveling before metastasis can occur.

Fundamental sequence of events in metastasis

Pre-metastatic niche 1 (PMN-1) (**FIGURE 2**)

PCN transforms into a local PMN-1 involving cancer cell development and an increase in CAFs and subsequent cancer growth and angiogenesis, thereby ensuring cancer cell nutrition and lymphogenesis for the necessary lymphatic drainage. This serves for the growth of cancer cells, but also in parallel as a proclivity for metastasis. Ongoing mesenchymal-epithelial transition (MET) in CAFs increases cancer cell numbers and growth, with heterogeneous CAFs and pools of cancer cells.

CAFs and LOX signaling induce crosstalk between FAK and p130(cas)-Src-Crk and formation of the p130(cas)/crk/DOCK180 complex, a necessary precursor for the formation of lamellipodia. Subsequently, lamellipodia enable cell mobility and motility and are a

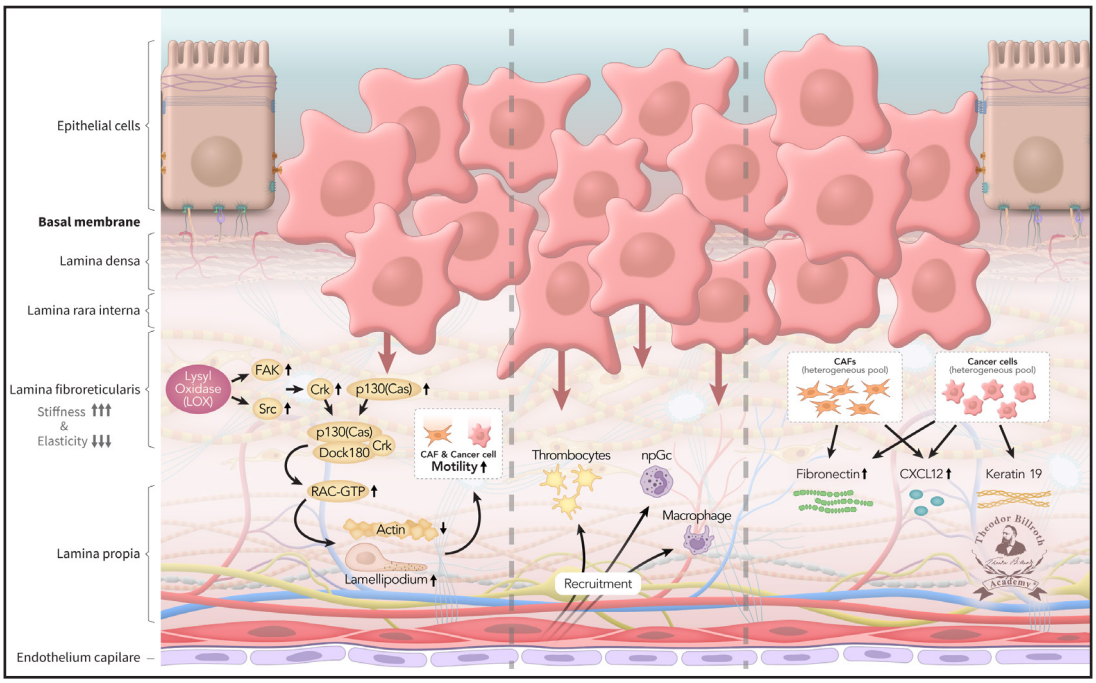

Fig. 2. Pre-metastatic niche 1 (PMN-1): With increasing disruption of homeostasis, the pre-cancerous niche transforms into a premetastatic niche 1 (PMN-1): the heterogeneous CAF cell pool together with lysyl oxidase by heterogeneous cancer cells induce p130(cas)/crk/DOCK180 complexes and, via RAC-GTP, increased lamellipodia, decreased actin fiber function, and enhanced cell motility and mobility. Decreased apoptosis and loss of cell-cell contact inhibition, reinforces cancer cell growth, and invasion of the basal lamina. CAFs begin to release fibronectin and CXCL12, and cancer cells release CXCL12 and Keratin 19. Platelets, neutrophils, and macrophages are increasingly recruited and later serve as prerequisites for pre-metastatic niche 2 (PMN-2) formation.

prerequisite for increasing migration toward the endothelium.

In parallel, an induced decrease in apoptosis (cell death), as well as loss of cell-cell contact inhibition, reinforces cancer cell growth, and encourages invasion of the basal lamina and subepithelial layers and subsequent population of the deeper stroma. This process is recognized in the TNM classification as T-stage evolution from T1 to T4.

Subsequently, additional fibroblasts are recruited, and CAFs increase and begin to release fibronectin and CXCL12 into the stroma, as well as Keratin 19. Platelets, macrophages, neutrophils, monocytes, and T-cells are recruited to the tumor microenvironment.

Pre-metastatic niche 2 (PMN-2) (**FIGURE 3**)

Pre-metastatic nice 1 (PMN-1) is transformed into PMN-2. Various subsets of tumor-associated cells (TACs), such as tumor-associated macrophage (TAMs), tumor-associated plateles (TAPs), and tumor-associated neutrophils (TANs), develop during ongoing signaling and crosstalk. Anti-tumorigenic TACs increasingly transform into pro-tumorigenic TACs with local immunosuppression and a lack of CD8+ T-cell immune evasion.

Furthermore, cancer cells, as well as CAFs, additionally induce the formation of neutrophil extracellular traps (NETs), which promote migration and metastasis, and are found in various epithelial cancer tissues, the vascular system, and distant metastases [**329**]. The CXCL12 and fibronectin gradients expand. Cell mobility is also facilitated by ongoing LOX-induced formation of lamellipodia, thus promoting cell motility. Blebbing and EVs further increase the motility and travel of CAFs and cancer cells. Meanwhile, increased fibronectin, CXCL12 release, and decreased F-actin result in formation of a CXCL12- and fibronectin-gradient, along which increasingly mobile cells migrate toward the endothelium as a step towards travel away from the primary tumor.

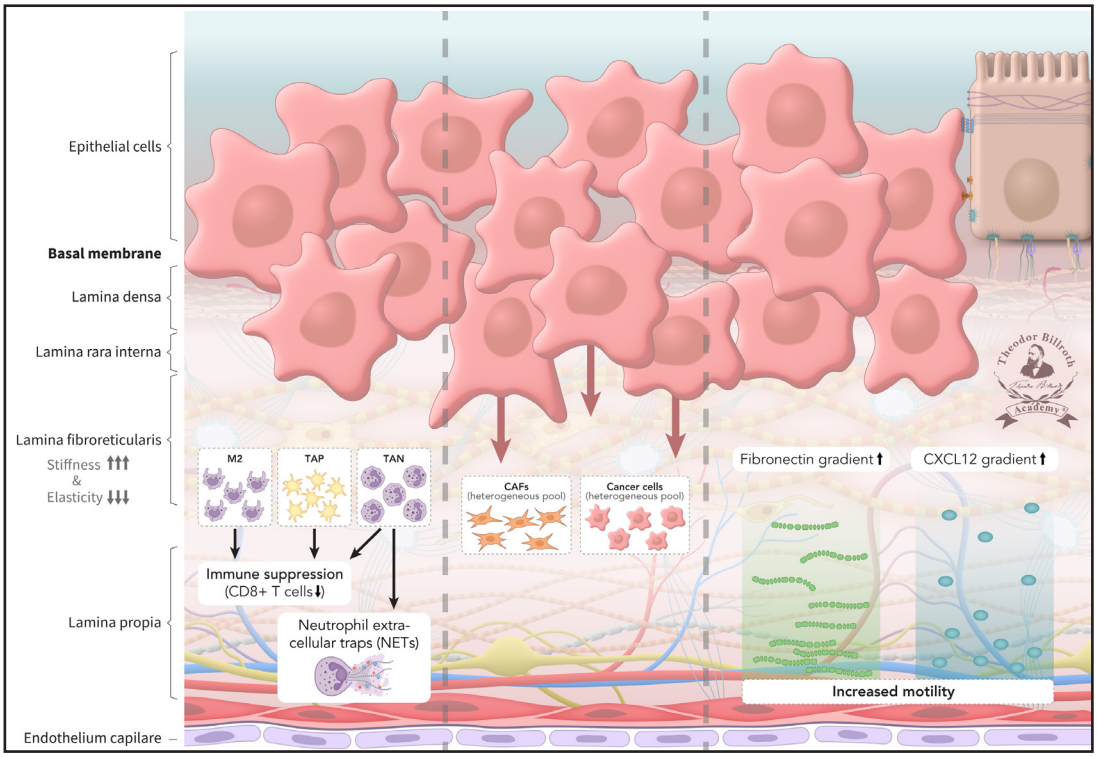

Fig. 3. Pre-metastatic niche 2 (PMN-2): Various subsets of tumor-associated cells (TACs), such as tumor-associated macrophages (TAMs), tumor-associated platelets (TAPs), and tumor-associated neutrophils (TANs), develop during ongoing signaling and crosstalk. Anti-tumorigenic TACs increasingly transform into pro-tumorigenic TACs with local immunosuppression and a lack of CD8+ T-cell immune evasion. Neutrophil extracellular traps (NETs) from TANs are increasingly released, and heterogeneous CAFs and cancer cell pools develop. The graphical icon of NETs in Figure 4 was adapted with modifications from prior research [329].

Pre-metastatic niche 3 (PMN-3) (**FIGURE 4**)

PMN-2 transforms to PMN-3 as further disruption of homeostasis occurs, and serves as a prerequisite for metastasis. The evolution of the pre-metastatic niche (PMN) leads to PMN-3, in which intravasation of cancer satellites, involving trans-endothelial migration, provides access to the vascular system. This process is recognized in the TNM classification as further cancer evolution with hematogeneous (V), lymphatic (L), and perineural (Pn) invasion. Transendothelial migration alone is complex with its adhesion (Supplement, part 18, E-, P-, and L-selectin).

PMN-3, according to current knowledge, comprises eight cancer satellites, which access intravasation and subsequently travel (or, as usually described, "circulate") far from the primary tumor. The fundamental prerequisites for metastasis are met by eight cancer satellites, including Trojan horses, which enable immune escape, as follows: (1) Cancer cells and (2) CAFs both migrate along the CXCL12 and fibronectin gradient. (3) CAFs surround cancer cells and migrate. (4) CXCL12 and Keratin 19 coated cancer cells migrate. (5) CAFs and (6) cancer cells are surrounded by platelets and migrate. (7) Neutrophils form NETs that shield CAFs and (8) cancer cells, thus facilitating migration and traveling.

The dissemination of cancer satellites is not synonymous with metastasis despite often being described as such. It sets the stage for later metastases. Maybe even M2 macrophages surround CAFs and cancer cells. However, cancer cells are surrounded by CAFs [**330**]. Platelet inhibition decreases metastasis and cancer cell adherence to platelets via P-selectin [**214, 331**]. Cancer cells are surrounded by platelets [332], which impede natural killer cell-mediated elimination of tumor cells [**333**]. Therefore, various cancer satellites to facilitate metastasis are created.

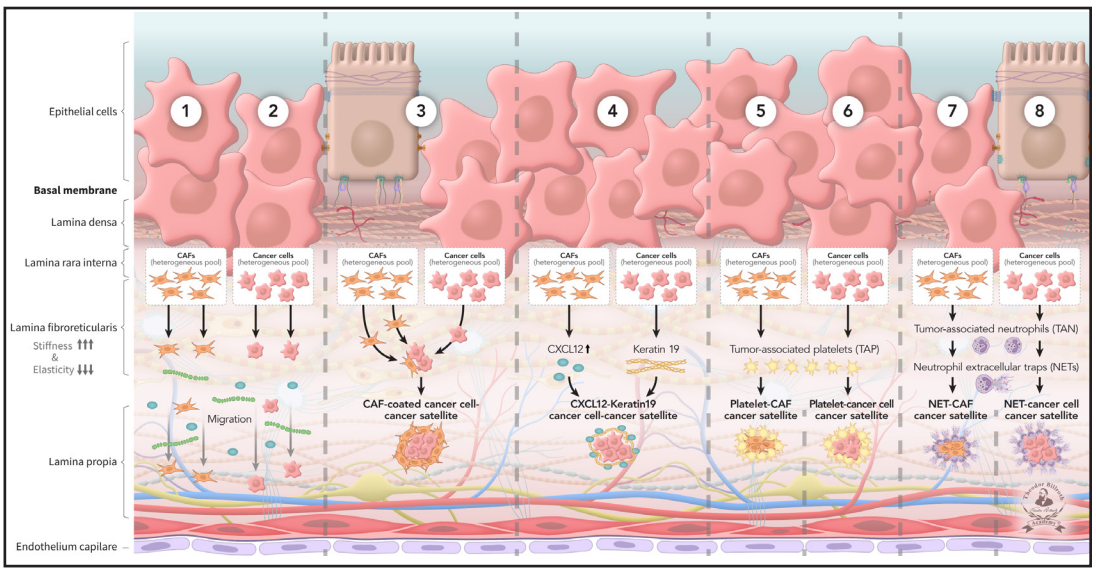

Fig. 4. Pre-metastatic niche 3 (PMN-3): Metastasis in epithelial cancer occurs in parallel with carcinogenesis after the pre-cancerous niche transformed into pre-metastatic niches (PMNs), which are indispensable to the origin of metastasis. Pre-metastatic niche 2 (PMN-2) transforms to pre-metastatic niche 3 (PMN-3) by ongoing signaling and crosstalk. PMN-3 serves as prequisite for intravasation, traveling, and how metastasis arises. According to current knowledge, a series of eight heterogeneous cancer satellites develop, including Trojan horses (immune evasion), alongside reciprocally affecting sequences, and subsequently travel (or, as usually described, "circulate") alone or in combination, far from the primary tumor. The fundamental prerequisites for metastasis are met as follows: (1) Cancer cells and (2) CAFs both migrate along the CXCL12 and fibronectin gradient. (3) CAFs surround cancer cells and migrate. (4) CXCL12 and Keratin 19 coated cancer cells migrate. (5) CAFs and (6) cancer cells are surrounded by platelets and migrate. (7) Neutrophils form neutrophil extracellular traps (NETs) that shield CAFs and (8) cancer cells, thus facilitating their migration and traveling.

As neutrophils surround cancer cells or CAFs they expel NETs, together with nuclear histones, and granular and cytoplasmic proteins [**334–336**]. NETs facilitate liver metastasis [**337**], and have been observed in gastric, liver, and pancreatic cancers [**337–339**], as well as other epithelial cancers. Moreover, NETs aid in building clusters with growth at the peritoneal in gastric cancer [**277, 340**].

Pre- and malignant cells and various aggregates with various metastatic capabilities have been found in cancer nodules and observed to have high heterogeneity [**341, 342**]. These findings might explain why both single cells and clusters of cancer cells have been detected in cancer blood samples [**343**]. Platelet-cancer cell cancer satellites are fundamental for metastasis. The cancer satellites created from platelets with cancer cells and CAFs explain also early reports of local recurrence, such as that observed 19 years after resection of a primary tongue carcinoma or a long-term course in a breast cancer with a duration of 15 years in 1885 [**344**].

Metastasis is a complex phenomenon. After transendothelial migration, cancer satellites travel and if not eliminated by the immune system, extravasate after arriving at vascular endothelial capillaries. Furthermore, when cells grow, transendothelial migration occurs synchronously with local micro-metastasis, i.e., the metastatic colonization observable under a microscope.

Implications

A brief overview of implications to minimize or prevent metastasis is as follows:

As discussed, in patients with cancer, platelet aggregation and inhibition should be considered immediately after diagnosis.

This approach could also be used to mitigate the potential for metastasis.

Even patients post surgery should receive a low molecular anticoagulation regimen to inhibit platelet aggregation. The drugs should be coated to facilitate resorption in the jejunum and minimize gastric adverse effects.

Anti-inflammatory therapy: a much more effective anti-cancer therapy approach would balance the treatment with an anti-chronic inflammatory regimen.

Anti-fibrotic therapy: a much more effective anti-cancer therapy approach would include an anti-fibrotic regimen.

Although measured and observed daily worldwide, changes in the values of platelets, macrophages, neutrophils, monocytes, as well as other immunocompetent cells, are interpreted primarily as adverse effects of multimodal therapy. However, as described herein, these routine laboratory parameters could be used to create models to predict cancer progression and the potential for metastasis before it occurs.

Current cancer treatment regimens comprising multimodal therapy with chemotherapy and/or combined immune therapy and/or radiotherapy protocols. These can lead to thrombocytopenia, leukocytopenia, neutropenia, and monocytopenia, as well as decreases in macrophages and other immunocompetent cells, such as T-cells, as well as TACs. Therefore, whether therapy regimes used over several decades might be largely effective in terms of anti-cancer effects, and/or in which percentage ranges induced by these standard-of-care regimens or might have promoted metastatic development, because of their cytotoxic effects on the cells listed, remains unknown.

Real-world data on the anti-cancer effects of multimodal treatment protocols must measure each cell type together with TACs to determine whether the therapies are effective or largely reflect the adverse effects of therapy, such as decreasing TACs with observed, if minimal, anticancer effects.

This would apply to CAR-T therapy as it affects each cell type.

Applying such strategies in cancer surgery would be a challenge, because detailed understanding of inflammatory and fibrosis and its remodeling [**3, 14–19, 127**] is necessary: performing surgery too early might severely affect postoperative wound healing. Therefore,

in pre-cancer surgery: anti-inflammatory and/or anti-fibrotic approaches should not be performed 4 weeks pre-surgery, to avoid adversely affecting post-surgery wound healing.

Post-cancer surgery: both anti-inflammatory and/or anti-fibrotic approaches would require an uneventful post-surgery course and a time delay of at least 4 weeks postoperatively (particularly for critical anastomosis).

Knowledge and understanding of molecular signaling are continually increasing. The fundamental complexity of how metastasis arises could not have been observed or recognized previously, because of the reasons discussed above.

The achievements of the giants, on whose shoulders we stand, are available but less widely taught. Although many possible explanations exist, education has increased overall, but the emphasis on basic sciences has decreased. Subjects such as biochemistry and physiology are nearly globally underemphasized in the education of scientists and physicians.

For example, in human medicine, the field in which clinicians and scientists treat patients with cancer, popular ideas have been implemented. The teaching content for, e.g., biochemistry and physiology has already decreased by nearly 50% under the rubric of the so-called new (modern) medical course model (German: Modelstudiengang). This new way of teaching has been described as an innovative approach blurring traditional disciplinary boundaries and achieving an integrated practice-oriented approach for future scientists and physicians. However, the warnings raised in many disciplines were ignored and subsequently went silent, and the propagated declarations louder, especially, we argue in spiritu to Billroth, that scientists keep both eyes on the past go blind, but in science, keeping on eye on the past, may allow us to be more critical. Giulio Bizzozero (1846–1910) has already taught us that, in science approximately 150 years ago, "*the teacher should not present science as a series of dogmas supported by the prestige of a name [...] but instead expose it in its true condition, with its doubts and its questions*" [English translation] [**345**].

Genetic and stem cell research have greatly influenced current knowledge and thinking, and have been essential to many achievements in science. Over approximately 100 years, the focus on promoting success in cancer and metastasis has been on genetics, while cancer incidence has continued to increase [**4**]. However, as clearly indicated, neither somatic mutation theory nor stem cell theory can explain carcinogenesis [**4, 5**] or metastasis [Authors' note: we have omitted to cite the abundant literature on this topic, as it is available here: **5**].

Additionally, a major paradoxical transformation occurred through misinterpretation of correct statistical analysis, such that the data were incorrectly interpreted to be the cause of cancer and metastasis.

One non-genetic example of the global cancer burden is the predicted increase in gastric cancer incidence [**346**]. However, there might be an incorrect focus on the gastric cancer diagnostics market, which has been predicted to increase within the next 10 years, to USD 970.95 million by 2034 [**347**].

Declarations that somatic mutations are "the" cause of cancer and metastasis have not helped materially to date and are extensively reviewed earlier [**5**].

Aspects that cannot be explained are regularly phrased by statements such as "we assume some aspects of genetics remain unknown"; more concerningly, most editors accept such sentences. A quotation by Mechtilde Lichnowsky (1879–1958) from 1924 still resonates:" Nothing *is easier to learn than the art of approximation, nothing succeeds so much, nothing prevails so convincingly, nothing is more stubborn in assertion, nothing is harder to unmask because of the false resemblance to genuine*" [English translation] [**348**].

A much more nuanced and differentiated way is psychologically contrary to a more realistic but complex explanation, possibly because binary views are easy to accept, believe, and propagate (*please see "marketing and perception" in* [**4**]).

In Summary

The thought processes described herein suggest new previously underappreciated aspects of most epithelial cancers and how they metastasize. Cancer can now be considered a parasite, developed from one's own cells, which lives in and harms its host by actively transforming host cells into cancer cells. Various cell compartments are subverted, thereby enabling cancer cells to undergo transendothelial migration and travel to distant parts of the body (metastasis), with markedly increased mortality.

Cancer and metastasis are, in essence, states of disruption of homeostasis. The complex framework of cell-to-cell communication, including signaling and crosstalk, highlights a series of sequences positioned in relation to each other. The pre-cancerous niche (PCN) during carcinogenesis is transformed through ongoing disruption of homeostasis, thus leading to the evolution of pre-metastatic stages.

A series of eight heterogeneous cancer satellites, including Trojan horses to enable immune evasion, alongside reciprocally affecting sequences, develop, which are indispensable for intravasation, traveling, and mixed dissemination (metastasis). In parallel, the main multimodal anti-cancer cell effects can now be seen in a new, previously unrecognized light. The benefits might rely not on direct cancer cell effects but on indirect cytopenic effects, which, to date, have been regarded merely as adverse effects.

Multimodal therapy in cancer, including metastatic cancer, interferes with the anti-cancer functions of platelets, macrophages, and neutrophils, and further exacerbates disease progression and metastasis.

Consequently, these findings might provide a new explanation for why combinations of multimodal therapy can result in sudden observed efficiency, even in highly aggressive cancers, such as triple negative breast cancer [**349**], which are subseqzently lost.

To date, studies on cytotoxic multimodal therapy efficiency in the past 50 years have focused on observed effects of cancer cells, diminished cancer nodule growth in imaging, and decreases in cancer cells and variables (such as prolonged time to recurrence and disease-free survival), despite only minimal effects on overall survival. Now, a clearer understanding of metastasis provides opportunities to treat cancer at multiple points, and to block or even mitigate metastasis.

Consequently, multimodal treatments in patients with epithelial cancers cannot achieve healing, but can only slow disease progression until drug resistance or death occurs. Therefore, homeostasis is not merely a figurative term but clearly has a basis in multiple biochemical, physiological, and pathophysiological pathways. Given the known high redundancy in nature, and that homeostasis involves a balance among processes within the body to maintain a state of health, additional cancer satellite complexes are likely to be found and reported in the future.

Should Theodor Billroth's (1829–1894) quotation from 1883, "*The completeness of a textbook always remains an illusion [...]*" [English translation] [**350**], or from 1881, "*Everyone sees the world only from their own perspective, considers themselves to be the center around which everything emerges*" [English translation] [**351**], be invoked as excuses? Or is it the cancer research community, writ large, that has been on the wrong path?

Friedrich Schiller (1759–1805), in 1796 [**352**], stated: "*What's the hardest of all? What you think is the easiest, to see with your eyes what's in front of your eyes*" [English translation]. This quotation applies not only to the long time not seen origin of the first derived epithelial cancer cell. Although it was recognized by Rudolf Virchow (1821–1902) in 1856 [**353**], more than a century was required to address it, on the basis of current knowledge of signaling and crosstalk, and the identification of a mesenchymal cell precursor of the first cancer cell [**15**].

Scientific progress regarding cancer and metastasis has been slowed by a viewpoint in which all its solutions are seen from solely a genetic perspective, and a symptom-based therapeutic approach is followed.

The understanding of carcinogenesis and metastasis can no longer be viewed so myopically. The efficiency of many currently applied therapies must be re-visited by

addressing the aspects described herein. Many clinically and experimentally observed adverse effects due to cytotoxic therapies are likely to be the reason for anti-metastatic efficiency. Therefore, cytotoxic therapies in epithelial cancers are often associated with transient (i.e., time-limited) responses and lower metastatic rates, but not patients' quality of life and rarely long-term survival.

Conclusion

Many great successes have been achieved in healthcare and science in the past 200 years [**4**]. However, success in most epithelial cancers, despite being discussed daily in the media, have remained marginal. Survival continues to be reported in weeks or months, yet is reported as "breakthroughs." The theories of how metastasis occurs consist of vascular and embolic genesis, the seed and soil theory, CTCs, and others [**5**] (Supplement, part 2–4) which are insufficient to explain metastases as documented in this paper.

We addressed the fundamental questions in cancer biology between 2014 and 2022, regarding how most cancers (80.5% epithelial) develop (Epistemology of the Origin of Cancer I) [**3, 5, 14, 16–19, 127**] and which is the first cancer cell (Epistemology of the Origin of Cancer II) [**15**]. In essence, carcinogenesis is a disruption of homeostasis. More specifically, the persistent disruption of homeostatic crosstalk by (1) ongoing pathogenic stimuli leads to (2) chronic inflammation, which is followed by (3) fibrosis and (4) remodeling to a PCN. If this step is unresolved, chronic tissue stress in the PCN results in an escape strategy, (5) CSES (**FIGURE 1**). To resolve the CSES and restore homeostasis, a heterogeneous fibroblast pool is recruited, which then undergoes EMT. Consequently, a heterogeneous pool of CAFs develops and undergoes (6) MET. These CAFs express epithelial markers, which facilitate their integration into the target tissue. This process explains why, later in carcinogenesis, cancer cells "appear" as an epithelial type (*Please see figures 1 to 3 in* [**15**]). This neoplastic transformation to a cancerous phenotype also explains the heterogeneity of tumors.

The third unanswered basic question in cancer biology pertains to the fundamentals of how metastases begin. Here, we demonstrated the further breakdown of homeostasis, in all its elegant complexities, to highlight the critical roles of pre-metastatic niches (PMNs) (**FIGURE 2 and 3**), together with cancer satellites, in transforming various cell compartments into Trojan horses enabling cancer cells and CAFs to successfully evade the immune system (**FIGURE 4**).

Whether the newly reported organelle structures called hemifusomes—which consist of two vesicles, one larger (~300 nm) and one smaller (~150 nm), partially fused via a thin, lens-shaped membrane (hemifusion diaphragm) [**354**]—have roles in cancer and/or metastasis is not currently known. However, we would not be surprised if such a role were discovered.

The findings described herein and in the supplement are summarized in **FIGURE 4** to illustrate a complex but plausible explanation for how metastasis in epithelial cancer occurs in parallel with carcinogenesis after the pre-cancerous niche is transformed into pre-metastatic niches (PMNs), which are indispensable in the origin of metastasis. Eight heterogeneous cancer satellites develop, including Trojan horses responsible for immune evasion, alongside reciprocally affecting sequences, travel alone or in combination, far from the primary tumor. The fundamental prerequisites for metastasis are met as follows: (1) cancer cells and (2) CAFs migrate along the CXCL12 and fibronectin gradient; (3) cancer cells surrounded by CAFs are shielded from the immune system and consequently travel away from the primary cancer; (4) CXCL12 and Keratin 19 coat cancer cells; (5) platelets surround cancer cells and (6) CAFs, thus facilitating cancer spread; and (7) neutrophil extracellular traps shield cancer cells and (8) CAFs.

Not all questions are answered in detail because of the complexity of the processes involved. Of course, new questions will arise from new thinking on this topic. However, these findings explain not only the heterogeneity of clinical and experimental findings, but also

the marginal benefits of existing anti-cancer treatments observed to date, in terms of patient survival measured in weeks or months, and why the cancer community remains far from developing anticancer treatments that measure patient survival in years with improcements in quality of life.

Metastasis, like carcinogenesis, occurs through a persistent disruption of homeostatic crosstalk, and the direction of shifts at any given point is critical

Cancer research must be less dogmatic and decrease emphasis on therapies that show significant p values, while placing greater emphasis on ameliorating the lives of patients with metastatic cancer. Much of the existing understanding of cancer biology, particularly metastasis, represents modest gains despite substantial effort. Therefore, as Johann Wolfgang von Goethe (1749–1832) stated, the content provided is just a part of a detour: "*Science, as a whole, always moves away from life, and only returns to it through a detour*" [English translation] [**355**].

Abbreviations

5-oxo-ETE (6E,8Z,11Z,14Z)-5-oxoicosa-6, 8,11, 14-tetraenoic acid; **12-HETE** 12-hydroxyeicosatetraenoic acid; **20-HETE** 20-hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,14Z)-20-hydroxyicosa-5, 8,11, 14-tetraenoic acid; **20-OH-PGE2** 20-hydroxy prostaglandin E2; **^{125}IUDR** ^{125}I-iodo-2´-deoxyuridine; **αSMAD** alpha-smooth muscle actin; **A1BG** alpha-1-B glycoprotein; **ALOX** lipoxygenase, arachidonate lipoxygenase; **ALOX5** 5-lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase; **ALOX12** 12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type; **AP1** activator protein 1; **ARG1** arginase 1; **ASGR1** asialoglycoprotein receptor 1; **ASGR2** asialoglycoprotein receptor 2; **B7-1** cluster of differentiation 80 (CD80); **BIM** Bcl-2 interacting mediator of cell death; **CAF** cancer-associated fibroblast; **CC** cancer cell; **CCC** cholangiocellular carcinoma; **CD8+ T-cells** MHC class I-restricted T-cells; **CD47** cluster of differentiation 47; **CD74** cluster of differentiation 74; **CD80** cluster of differentiation 80 (B7-1); **CD97** cluster of differentiation 97; **cdc42** cell division control protein 42 homolog; **cdk2** cyclin-dependent kinase 2; **CIS** carcinoma in situ; **COMP** cartilage oligomeric matrix protein; **Cox** cyclooxygenase; **Cox-1** cyclooxygenase 1; **Cox-2** cyclooxygenase 2; **Cox-3**: isoform of Cox-2 (therefore in brakes); **CRC** colorectal cancer; **CS** cancer satellite complex; **CSES** chronic stress escape strategy; **CTC** circulating tumor cell; **CXC CC** chemokine receptors; **CXCL1** chemokine (C-X-C motif) ligand 1; **CXCL12** chemokine CXCL12 (stromal cell-derived factor 1, SDF-1); **CXCR4** C-X-C motif of chemokine receptor 4; **CYP*** cytochrome P450 isoforms; **DOCK180** dedicator of cytokinesis; **DMBA** 7, 12-dimethylbenz [a]anthracene; **E2F4/5** cytoplasmic complex of Smad3, retinoblastoma-like protein 1 (P107, RBL1), E2F4/5 and D-prostanoid (DP1); **E-cadherin** CAM 120/80 or epithelial cadherin, cadherin-1, epithelial cadherin; **Egfl7** EGF-like domain multiple 7; **EMT** epithelial-mesenchymal transition; **ERK2** extracellular signal-regulated kinase 2, mitogen-activated protein kinase 1, MAPK1; **ESCC** esophageal squamous cell carcinoma; **EV** extracellular vesicle; **FADS2** fatty acid desaturase 2 (FADS2, ω-6-desaturase, D6D); **FAK** focal adhesion kinase; **FAP** fibroblast activation protein, surface gelatinase; **FOXO3a** forkhead box protein O3a; **FSP-1** fibroblast specific protein-1; **GPCR** adhesion G protein-coupled receptor (high-mobility group box 1, HMGB1); **HCC** hepatocellular carcinoma; **IFNγ** interferon gamma; **iNOS** nitric oxide synthase; **IL-6** interleukin 6; **IL-8** interleukin 8; **IL-β1** interleukin beta 1; **IL-33**: interleukin 33; **JAM-1** junctional adhesion molecule-1; **LPS** lipopolysaccharide; **LTA4** leukotriene A4, 4-[(2S,3S)-3-[(1E,3E,5Z,8Z)-tetradeca-1, 3,5, 8-tetraenyl]oxiran-2-yl] butanoic acid; **LTB4** leukotriene B4, (5S,6Z,8E,10E,12R,14Z)-5, 12-dihydroxyicosa-6, 8,10, 14-tetraenoic acid; **LTC4** leukotriene C4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-[[(4S)-4-amino-4-carboxybutanoyl]amino]-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,

9,11, 14-tetraenoic acid; LTD4: leukotriene D4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7, 9,11, 14-tetraenoic acid; **LTE4** leukotriene E4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-2-carboxyethyl]sulfanyl-5-hydroxyicosa-7, 9,11, 14-tetraenoic acid; **LOX** lysyl oxidase; **LOXL3** lysyl oxidase homolog 3; **LRP1** low-density lipoprotein receptor-related protein 1; **M1 MO** classically activated M1 macrophages; anti-tumorigenic phenotype; **M2 MO** alternately activated M2 macrophages; pro-tumorigenic phenotype; **M** metastasis; **MAPK1** mitogen-activated protein kinase 1, extracellular signal-regulated kinase 2, ERK2; **MDA** malondialdehyde, propanedial; **MDSC** myeloid-derived suppressor cells; **MET** mesenchymal epithelial transition; **miR21**: microRNA-21; **MMP-1**: matrix metalloproteinase 1; **MMP-2** matrix metalloproteinase 2; **MMP-7** matrix metalloproteinase 7; **MMP-9** matrix metalloproteinase 9, gelatinase B; **MO** macrophage; **MSCs** mesenchymal stem cells; **mTORc1** rapamycin complex 1; **MZF1** myeloid zinc finger 1; **N** neutrophil; **N1** anti-tumorigenic neutrophil phenotype; **N2** pro-tumorigenic neutrophil phenotype; **NCCCT** normal cell to cancer cell transition; **NETs** neutrophil extracellular traps; **NF-κB** nuclear factor kappa-light-chain-enhancer of activated B cells; **NMII** non-muscle myosin II; **NRP1** neuropilin-1; **Osm** oncostatin-M; **p107** retinoblastoma-like protein 1, RBL1; **p120** catenin delta-1, protein 120; **p130(cas)** breast cancer anti-estrogen resistance protein 1, BCAR1; **p300** protein 300 (p300-CBP coactivator family); **P** platelets (thrombocytes); **PAR1** proteinase-activated receptor 1; **PAI1** plasminogen activator inhibitor-1; **PCN** pre-cancerous niche; **PDGF** platelet-derived growth factor; **PGD2** prostaglandin D2, (Z)-7-[(1R,2R,5S)-5-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid; **PGE2** prostaglandin E2, (Z)-7-[(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid; **PGFF2α** prostaglandin F2 alpha, (Z)-7-[(1R,2R,3R,5S)-3, 5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid; **PGG2** prostaglandin G2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroperoxyoct-1-enyl]-2, 3-dioxabicyclo [2.2.1]heptan-6-yl]hept-5-enoic acid; **PGH2** prostaglandin H2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroxyoct-1-enyl]-2, 3-dioxabicyclo [2.2.1]heptan-6-yl] hept-5-enoic acid; **PHA1** prolyl-4-hydroxylase A1; **PI3K** phosphatidylinositide 3-kinase; **PMN-1** pre-metastatic niche 1; **PMN-2** pre-metastatic niche 2; **PMN-3** pre-metastatic niche 3; **Pro-MMP-1** pro-matrix metalloproteinase 1; **Pro-MMP-7** pro matrix metalloproteinase 7; **Pro-MMP-9** pro-matrix metalloproteinase 9; **PSAP** prosaposin; **PUMA** BH3-only protein; **Rac1** Ras-related C3 botulinum toxin substrate 1; **Rho** Ras homolog gene family, member A; **ROCK** Rho-associated coiled-coil kinase; **ROS** reactive oxygen species; **S1P** sphingosine-1-phosphate; **SALL4** Sal-like protein 4; **SNAIL** zinc finger protein SNAI1; **SOX** [sex-determining region Y (Sry) box-containing] transcription factor family; **SP1** specificity protein 1; **SphK** sphingosine kinase isoform; **TAC** tumor-associated cell; **TAM** tumor-associated macrophage; **TAN** tumor-associated neutrophil; **TAP** tumor-associated platelet; **TGFβ** transforming growth factor beta; **TIMP-1** tissue inhibitor of metalloproteinases-1; **TLR4** Toll-like receptor 4; **TNFα** tumor necrosis factor alpha; **TReg** CD4+ T-helper cells; **TSP-1** thrombospondin-1; **TXA2** thromboxane A2, (Z)-7-[(1S,2S,3R,5S)-3-[(E,3S)-3-hydroxyoct-1-enyl]-4, 6-dioxabicyclo [3.1.1]heptan-2-yl]hept-5-enoic acid; **YAP** yes associated protein.**)**.

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