

Review

Epistemology of the Origin of Cancer IV: Predisposing Conditions for Metastases

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Key Words

Metastasis • Signaling • Crosstalk • Carcinogenesis • Heterogeneity

Abstract

Causal therapy has achieved success in the treatment of epithelial tumors, which account for more than 80% of all cancers. Although frequently claimed as breakthroughs, cancer therapy has achieved limited increases in survival of only weeks to several months, and cancer incidence continues to increase and metastasis rates, which are primarily responsible for cancer mortality, remain constant. This broadly reflect an incomplete understanding of the genesis and progression of cancers and metastases. Over a 25-year timeframe, the fundamentals of the origin of carcinogenesis and metastasis, titled Epistemology of the Origin of Cancer were addressed in Part I, 2014–2022, how carcinogenesis develops; Part II, 2023, which is the first cancer cell; Part III, 2025, how metastasis arise with the formation of local pre-metastatic niches (PMN-1, PMN-2, PMN-3) and traveling cancer satellites. Herein, Part IV discusses the conditions required for metastasis: the development of distant metastatic niches (MN-1, MN-2, MN-3) after traveling, extravasation and nidation at the endothelium of the capillary bed. First, MN-1 develops by transendothelial migration of cancer satellites to the subendothelial matrix, followed by de-coating into constituent parts, induction of cell plasticity, recruitment of immuno-competent cells, and dormancy. MN-1 then transforms into MN-2 triggered by ongoing chronic inflammation, and remodeling (lysyl oxidase): pro-tumor-associated cells, extravesicular vesicles, and CXCL2 induce immune suppression, granulins, periostin, fibronectin, CXCL12, and K19 followed by migration of non-dormant cancer associated fibroblasts (CAFs) and cancer cells. Finally, MN-3 develops where high cell plasticity leads to more aggressive active elongated cancer cells and newly developed metastasis-associated fibroblasts (MAFs), which re-trigger dormancy. Anticancer therapy, surgery, trauma, and ongoing inflammation exacerbate immune suppression, which induce awakening from dormancy. Gelsolin and atypical EMT induce conversion into spherical, inactive cancer cells (enabling immune evasion), followed by another spell of dormancy. When overwhelmed, this can lead to the essential predisposing conditions for

metastases by formation of metastatic cancer satellites: (1) metastatic cancer cells and (2) CAFs; (3) metastatic cancer cells surrounded by CAFs; (4) CXCL12 and K19 coated metastatic cancer cells; (5) platelets surrounding metastatic cancer cells and (6) CAFs; (7) NETs shielded metastatic cancer cells and (8) CAFs. The sequential distant metastatic niche model can serve as a coherent framework to better understand metastatic progression: metastatic cancer satellites, each with its distinct biology, are shielded from the immune system, and consequently migrate to distant sites, which fulfills the predisposing conditions for metastases. Analogously it provides biological meaning to long observed phenomena so far not satisfactorily explained: metastasis occurs concurrently with carcinogenesis; vast molecular and clinical heterogeneity; most disseminated cancer cells remain dormant for years; surgery or anticancer therapy can paradoxically trigger relapse; oncology therapies, despite direct anti-cancer cellular effects, have so far failed to substantially alter the natural history of most epithelial cancers.

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Graphical Abstract – Highlights

Fig. 1. Metastatic niche 1 (MN-1) develops from pre-metastatic niches (PMNs): Cancer satellites extravasate after traveling and nidate at the capillary bed; after transendothelial migration, de-coating into constituent parts occurs together with epithelial-mesenchymal transition (EMT), mesenchymal-epithelial transition (MET), mesenchymal-mesenchymal plasticity (MMP), recruitment of immunocompetent cells, senescence, and dormancy.

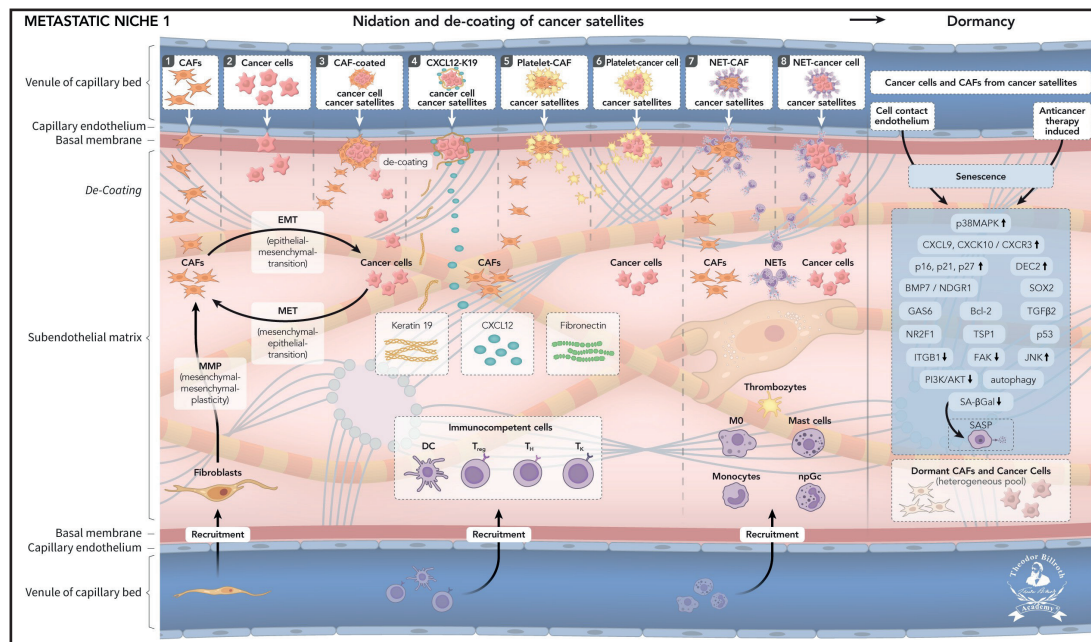


Fig. 1. Metastatic niche 1 (MN-1): Pre-metastatic niche 3 (PMN-3) 39, according to current knowledge, results in traveling of a series of eight heterogeneous cancer satellites develop, including Trojan horses (immune evasion), alongside reciprocally affecting sequences, and subsequently travel (or, as usually described, “circulate”) alone or in combination, far from the primary tumor: (1) Cancer cells and (2) CAFs both migrate along the CXCL12 and fibronectin gradient. (3) CAFs surround cancer cells and migrate. (4) CXCL12 and K19 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. These cancer satellites extravasate past traveling, and nidate at the capillary bed. After transendothelial migration, de-coating into constituent parts occurs, together with cell epithelial-mesenchymal transition (EMT), mesenchymal-epithelial transition (MET), and mesenchymal-mesenchymal plasticity (MMP), which further increase heterogeneity; recruitment of immunocompetent cells; senescence; and dormancy. In addition, because of endothelial cell contact, as well as applied anticancer therapy, heterogeneous subendothelial cells transform through senescence into dormancy; this transformation occurs through a complex signaling and crosstalk network involving p38MAPK, CXCL9, CXCL10/CXCR3, p16, p21, p27, DEC2, BMP7/NDGR1, SOX2, GAS6, Bcl-2, TGFβ, NR2F1, TSP1, p53, ITGB1, FAK, JNK, PI3K/AKT, autophagy, and dormancy.

Fig. 2. Metastatic niche 1 (MN-1) transforms into Metastatic niche 2 (MN-2): This transformation is induced by chronic inflammation, and remodeling through LOX with increased stiffness and decreased elasticity. LOX leads to increases in lamellipodia/motility. Recruited macrophages, platelets, and neutrophils lead to pro-tumorigenic TACs: TAMs (M2), TAPs, and TANs. CAFs secrete EVs and CCL2, thus leading to mesenchymal stem cells (MSCs), and immune suppression via decreased CD8+ T-cells and increased CD4+ TReg cells. These changes in the microenvironment result in consistent increases in granulysin, periostin, CXCL12, fibronectin, and K19, which further increase motility, and promote the migration of non-dormant CAFs and cancer cells.

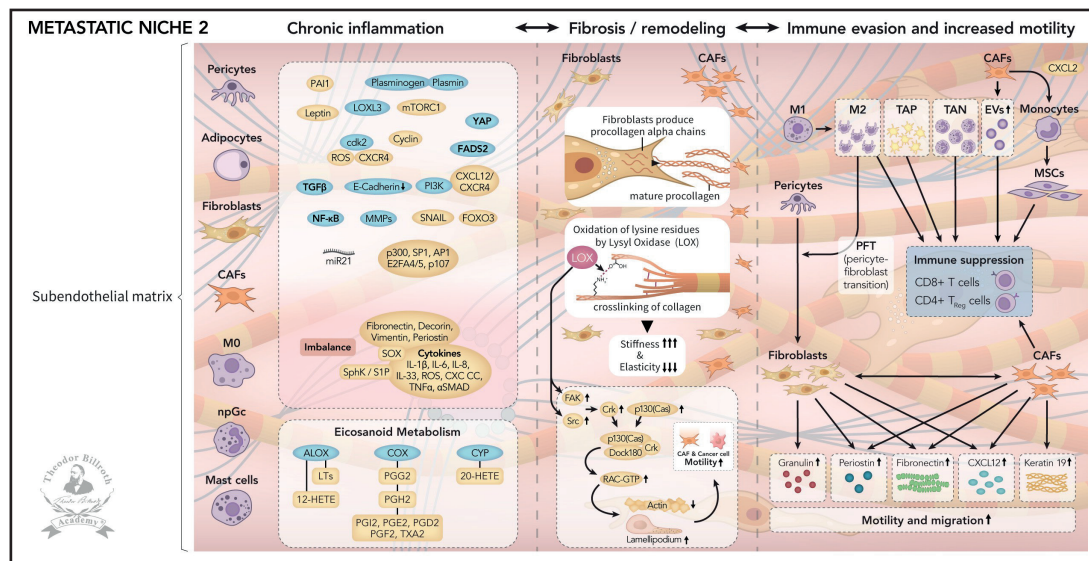


Fig. 2. Metastatic niche 2 (MN-2): Ongoing signaling and crosstalk increase recruitment of pericytes, adipocytes, fibroblasts, CAFs, macrophages, neutrophils, and mast cell induced complex chronic inflammation via TGFβ, E-cadherin, NF-κB, PI3K, Snail, FOXO3, CXCL12)/CXCR4, PAI1, mTORC1, ROS, ck2, YAP, FADS2, miR21, p300, SP1, AP1, E2FA4/5, p107, fibronectin, decorin, vimentin, periostin, Sox, and cytokines (such as IL-1β, IL-6, IL8, IL33, ROS, IFNγ, TNFα, and αSMAD). This process includes activation of eicosanoid metabolism via CYP, COX, and ALOX to 20-HETE, PPG2, PGH2, PG12, PGE2, PGD2, PGF2, TXA2, LTs, and 12-HETE. The result is fibrosis with collagen crosslinking through oxidation of lysine residues (remodeling) via lysyl oxidase, followed by increased stiffness and decreased elasticity. This leads again to FAK, p130 (cas)/ crk/DOCK180 formation, with increased lamellipodia/motility. CAFs secrete extravesicular vesicles (EVs) and CCL2, with monocyte transformation into mesenchymal stem cells (MSCs). Each, together with pro-tumorigenic tumor-associated cells (TACs), e.g., TAMs (M2), TAPs, and TANs, results in immune suppression, through decreased CD8+ T-cells, and increased CD4+ TReg cells. Parallel increases in granulysin, periostin, CXCL12, fibronectin, and K19 further increase motility and migration.

Fig. 3. Metastatic niche 3 (MN-3) fulfills the predisposing conditions for metastases or triggers dormancy: Increased cell plasticity induces active elongated cancer cells and newly developed metastasis-associated fibroblasts (MAFs), thus re-triggering dormancy. Anticancer therapy induces dormancy awakening, gelsolin with atypical EMT to spherical non-active cancer cells. Increased heterogeneity leads to formation of metastatic cancer satellites and immune suppression: (1) metastatic cancer cells and (2) MAFs migrate along gradients; (3) metastatic cancer cells are surrounded by MAFs; (4) CXCL12 and Keratin 19 coat metastatic cancer cells; (5) platelets surround metastatic cancer cells and (6) MAFs; and (7) neutrophil extracellular traps (NETs) shield metastatic cancer cells and (8) MAFs.

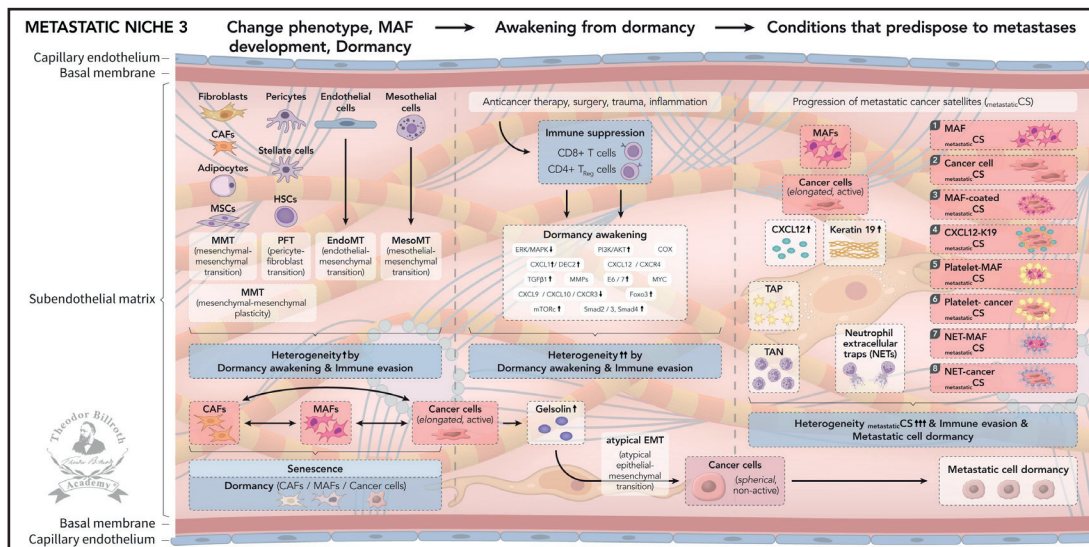


Fig. 3. Metastatic niche 3 (MN-3) involves increased plasticity with phenotype changes through mesenchymal-mesenchymal plasticity (MMP) via mesenchymal-mesenchymal transition (MMT), pericyte-fibroblast transition (PFT), endothelial-mesenchymal transition (EndoMT), and mesothelial-mesenchymal transition (MesoMT). These processes substantially increase heterogeneity, as well as CAFs' transition to MAFs and active elongated cancer cells, and again dormancy. Induced immune suppression, with decreases in CD8+ T-cells, and increases in CD4+ TReg cells, together with anticancer therapy, surgery, trauma, or inflammation, results in re-wakening from dormancy, followed again by increased heterogeneity. Increased gelsolin, through atypical epithelial-mesenchymal transition (atypical EMT), results in spherical non-active cancer cells. Finally, the conditions together with MAFs, cancer cells, CXCL12, K19, TAPs, TANs, and NETs are fulfilled for eight heterogeneous metastatic cancer satellites to develop, including Trojan horses (immune evasion): (1) metastatic cancer cells and (2) MAFs both migrate along the CXCL12 and fibronectin gradient. (3) MAFs surround metastatic cancer cells and migrate. (4) CXCL12 and K19 coated metastatic cancer cells migrate. (5) MAFs and (6) metastatic cancer cells are surrounded by platelets and migrate. (7) Neutrophils form neutrophil extracellular traps (NETs) that shield MAFs and (8) metastatic cancer cells. Consequently, increases in immune evasion and heterogeneity occur via metastatic cancer satellite dormancy.

Summary: Distant metastatic niches create high heterogeneity in CAFs, MAFs, and dormant and awakened cancer cells, which progress to form metastatic cancer satellites that fulfill the predisposing conditions for metastases.

Introduction

Living conditions in the Western world have improved, as reflected by an increase in life expectancy from approximately 40 years in the 1800s to approximately 60 years in the 1900s and approximately 80 years at present [1]. The manifold reasons for this include decreased infant and child mortality; improved hygiene, changes in work environments and fewer hazardous conditions, improved nutrition, and successful acute infection control through antibiotics, vaccination, and broad acceptance of scientific principles. The causes of death have shifted by improved medicine to chronic diseases, by enhancing the understanding, diagnosis, and treatment of chronic diseases, including cardiovascular diseases, diabetes, and, to a much lesser extent, cancer.

Cancer is the second leading cause of morbidity and mortality worldwide after infectious diseases. The greatest successes in treating cancer are achieved when the cause of cancer can be identified; examples include human papillomavirus-induced cervical cancer and oropharyngeal cancers, and hepatitis C-induced liver cancer. Further major accomplishments

have been made against leukemia, lymphoma, myeloma, melanoma, and pediatric cancers, which make up less than 10% of all cancers. Epithelial cancers account for approximately 80% of all cancers, and the success of their treatment, although heterogeneous, is measured by median survival of only weeks or months [2].

A recent meta-analysis examining the estimated life expectancy gains through cancer prevention, on the basis of 18 long-term randomized clinical trials involving 2.1 million individuals, has reported modest results, with little lifetime gain of days, with interventions such as sigmoidoscopy (110 days) mammography (0 days), prostate cancer screening (37 days), colonoscopy (37 days), fecal occult blood testing (0 days), and lung cancer screening (107 days) [3]. A study involving a randomized once-only sigmoidoscopy, with or without one fecal immunochemical test, or no screening in patients 50–64 years of age without colorectal carcinoma (CRC) at randomization, has indicated a cumulative 23-year CRC risk of 4.3% in the screened group and 6% in the unscreened group; adding fecal occult blood testing did not change screening benefits; otherwise, offering sigmoidoscopy decreased CRC risk by 1.7% (95% CI, -2.2 to -1.2 percentage points) [4]. Furthermore, CRC is the leading cause of cancer mortality in patients younger than 50 years [5]. These findings, together with markedly rising cancer incidence and nearly unchanged rates of metastases, illustrate the need to acknowledge that primary questions regarding the causal origins of cancer and metastases in epithelial cancers which have been ignored for too long.

Altogether, improvements in living conditions and their beneficial effects on increasing life expectancy should not be misinterpreted to suggest that the gains in life expectancy are due to better cancer therapies. Although adjusted epidemiological cancer mortality rates are helpful for comparison between patient groups in different regions or countries, they can provide a false sense of comfort [2]. Currently, age-adjusted cancer data are often touted as evidence of successes against cancer. However, age-adjusted cancer data should not be mistaken for precise measures, particularly when demographic changes occur over long periods, in which ages and outcomes do not remain consistent. Notably, when demographic shifts occur over long periods (e.g., in the current aging population), adjusted rates have diminished reliability, because underlying changes might potentially be masked. Therefore, age-adjusted data provide only a relative and hypothetical index, but are not an actual and precise measure. Consequently, considering age-adjusted data as evidence of success in cancer is not always as fruitful. The unadjusted cancer mortality rates in Germany and the USA over the past 80 years have remained relatively unchanged [2].

Genetics alone does not reliably predict most common diseases, mortality, or disease progression. Its predictive value is strongest in monogenic disorders, whereas most complex diseases arise from interactions between genetic susceptibility, environmental exposures, physiology, and stochastic processes. Biomarkers are not always reliable, and mismatch repair gene defects have clinical support in approximately 10%–15% of epithelial cancers, but not in the vast majority [6–28]. Although biomarkers are measurable, they do not necessarily indicate the presence of a disease, because nature maintains living systems in homeostatic balance. A measured biomarker can be completely unimportant in maintaining homeostasis and can contradict its function. Reducing a disease to one signal (i.e., a biomarker) may be inappropriate if the context of its function in signaling, and crosstalk is not also identified.

For example, a genome-wide association study in 124,682 individuals across eight longitudinal studies (FinnGen, UK Biobank, Estonian Biobank, Generation Scotland, Genomics England, Genes & Health, Dana–Farber Cancer Institute, and BioMe) examined nine diseases (CRC, prostate cancer, breast cancer, coronary artery disease, heart failure, type 2 diabetes, chronic kidney disease, Alzheimer disease, and stroke). Moreover, biomarkers, with the exception of those for certain rare cancers, are not reliable. Furthermore, twin studies were believed to be able to provide evidence of the genetic basis of cancers because monozygotic twins are genetically identical, whereas dizygotic twins share 50% of their genes. An analysis of 44,788 pairs of twins, one with and one without cancer in Swedish, Danish, and Finnish registries has assessed cancer risk at 28 anatomical sites. The twins without cancer had only a moderate absolute risk of having cancer at the same site as their twin with cancer [29].

Importantly, successes in only 10% of cancers, such as leukemia, lymphoma, myeloma, and melanoma, cannot and should not be extrapolated to most epithelial cancers, which have completely different tumor biology and conditions for disease progression and metastasis.

During a 25-year timeframe, the fundamentals of the origin of carcinogenesis and metastasis, titled *Epistemology of the Origin of Cancer*, were addressed. Part I, 2014–2022, discussed how carcinogenesis develops [16, 17, 20, 21, 30–35]. Most epithelial cancers develop in response to (1) a pathogenic stimulus that induces (2) chronic inflammation, which is followed by (3) fibrosis with remodeling, from which (4) a precancerous niche (PCN) develops. This sequence of events was later independently demonstrated in an animal model [36].

Part II, 2023, addressed which is the first cancer cell [37]. Our model suggests that fibroblasts may be the first cells to undergo neoplastic transformation. The precancerous niche (PCN) induces (5) a chronic stress escape strategy (CSES), including epithelial-mesenchymal transition (EMT) in epithelial cells, which leads to the differentiation of CAFs expressing both epithelial and mesenchymal markers; finally, (6) CAFs undergo mesenchymal-epithelial transition (MET), and epithelial markers facilitate integration into the epithelium. Fibroblasts are the initial precursors of cancer, as first stated on Apr 27, 1858, by Rudolf Ludwig Karl Virchow (1821–1902) [38].

Part III, 2025, addressed how metastasis arises [39]. The Recamier-Fuchs-Paget seed and soil theory [40–42] cannot explain metastasis, because only 0.2% of injected cancer cells survive after 2 weeks in the lung [43, 44], and 99.8% of cancer cells are effectively eliminated by the immune system. The circulating tumor cell (CTC) theory [45, 46] is not only incomplete but also cannot explain metastases. CTCs are not synonymous with metastases, because no characteristics of cancer cells predict aspects including metastatic potential, growth rate, and chromosome numbers; moreover, even highly metastatic cell clones do not necessarily grow faster than normal cells [47].

We have proposed that metastasis occurs in parallel with carcinogenesis after the PCN is first transformed into three premetastatic niches (PMNs) [39]. Here, we suggested the concept of cancer satellites in PMNs defined as: a cancer satellite is a cell or particle escorting another from one location to another more distant location [39]. We suggest, this applies to the creation of metastatic niches (MNs) as well, although there is still a knowledge gap, as some cancer satellites still require scientific verification. Otherwise, some cancer satellites had already been observed previously, but were not interpreted as such as in the manner proposed earlier [39], or here: platelets surround cancer cells followed by immune evasion [48, 49], and aggregate with cancer cells followed by immune evasion [50, 51]; anti-platelet aggregation by aspirin [52] or inhibition [53, 54] results into favorable prognosis and diminished clinically observed metastases; neutrophil extracellular traps (NETs) from tumor-associated neutrophils (TANs) wrap around cancer cells and protect such against immune attack [55]; CXCL12–Keratin-19 filamentous formation can coat cancer cells with immune evasion [56]; CAFs coat cancer cells and suppress T-cell infiltration by CXCL12 [57].

In pre-metastatic niche 1 (PMN-1), lysyl oxidase (LOX) induces focal adhesion kinase (FAK) and breast cancer anti-estrogen resistance protein 1 (p130(cas)/adaptor protein (crk)/dedicator of cytokinesis (DOCK180) formation, thus increasing lamellipodia and cell motility. CAFs and cancer cells secrete fibronectin and the chemokine C-X-C motif chemokine 12 (CXCL12, stromal cell-derived factor 1, SDF-1). Cancer cells also secrete Keratin 19 (K19), a prerequisite for increased migration. In parallel, platelets, neutrophils, and macrophages are recruited to PMN-1.

One important unanswered question pertains to the conditions necessary for metastasis to develop. Answering this question is complex, because the reason why greater heterogeneity is observed in metastasis than in the primary cancer must be explained in both clinical and molecular biological terms. The transformation from PMN-1 to pre-metastatic niche 2 (PMN-2) involves tumor associated cells (TACs) from tumor associated macrophages (TAMs), tumor associated platelets (TAPs), and tumor associated neutrophils (TANs), thus leading to the transformation of anti-tumorigenic TACs into pro-tumorigenic TACs,

local immunosuppression, a CXCL12 and fibronectin gradient, formation of lamellipodia, blebbing, and formation of neutrophil extravesicular vesicles (EVs), which together facilitate the mobility of CAFs and cancer cells, and allow them to migrate toward the endothelium.

PMN-2 transforms into pre-metastatic niche 3 (PMN-3), which serves as a prerequisite for metastasis. A series of eight heterogeneous cancer satellites develop, including Trojan horses (which facilitate immune evasion) and reciprocally affecting sequences that travel alone or in combination [illustration 3 in 39]. These satellites move along the fibronectin- and CXCL12 gradient, (1) cancer cells and (2) CAFs travel; (3) CAFs surround cancer cells and travel along the CXCL12- and K19 gradient; (4) CXCL12-K19-coated cancer cells migrate; platelets (5) surround CAFs and (6) cancer cells; and neutrophils form neutrophil extracellular traps (NETs), which (7) shield CAFs from immune attack and (8) allow cancer cells to migrate.

This sequence explains three important observations: (1) the logical associations found in patients with cancer after blood transfusion, (2) decreased disease-free time and survival, and (3) elevated metastasis rates, particularly in the context of TACs, because of transfusion-induced activation of TACs, particularly by TAPs. The current multimodal approach to cancer therapy can now be seen in a new previously unrecognized light. The benefits of such standard therapies might rely not on direct cancer cell effects but on indirect cytopenic effects, which have been regarded as merely adverse effects but can now be understood to interfere with the anticancer function of platelets, macrophages, and neutrophils, and to further exacerbate disease progression and metastasis. To gain a comprehensive understanding, closer examination of aspects of extravasation, such as capillaries, adhesion, soluble selectins, pericytes, and transendothelial migration, is necessary.

Extravasation, capillaries, and transendothelial migration

Readers are referred to the Supplemental materials for details regarding many aspects of signaling and crosstalk complexity and heterogeneity.

Extravasation

Extravasation is the exit of cancer cells from the vascular system at distant sites from the primary tumor location. Blood arrives at distant capillaries and consists of water; cell components; and plasma components such as albumin, fibrinogen, coagulation factors, globulins, electrolytes, nutrients (e.g., amino acids and lipids), hormones, metabolic waste, and oxygen. Blood is also the transport medium for other cells, such as CAFs, cancer satellites, and cancer cells, which have been observed by intravital videomicroscopy to arrive at the sinusoids of the liver and to arrest in narrow capillaries [58].

Platelet endothelial cell adhesion molecule (PECAM-1, platelet endothelial cell adhesion molecule, CD31) is found on many cells, such as endothelial cells, platelets, macrophages, lymphocytes, and Kupffer cells [59]. In an experimental model of hepatic metastasis based on splenic injection of CRC cells, the sinusoid location of Kupffer cells, fibroblasts, and PECAM-1 were revealed [60].

Capillaries

Capillaries consist of endothelial cells (in a single flat cell layer), a layer of connective tissue (basement membrane), and pericytes [61, 62]. Pre-capillary arterioles consist of the tunica intima, tunica media, and tunica adventitia, which post-capillary venules that consist of most endothelial cells. Capillaries in the human body consist of (1) non-fenestrated capillaries (skin, lung, brain), (2) continuous fenestrated capillaries (intestines), and (3) discontinuous capillaries (sinusoids) (liver and bone).

Before adhesion or transendothelial migration, cell-cell communication is necessary (**Supplement, part 1, Capillary signaling and crosstalk**). Selectins have previously been reviewed in detail [39]. Here, we discuss soluble selectins, which are important for adhesion

and nidation (**Supplement, part 2, Soluble selectins**). In this regard, phagocytic, contractile, and pluripotential pericytes function as sentinels of the distant tumor microenvironment (**Supplement, part 3, Pericytes**). After adhesion and nidation, transendothelial migration occurs.

Transendothelial migration

The transendothelial travel of immune cells occurs very rapidly. Laminin 511 is a bouncer, in that it stabilizes cadherin in between endothelial cells through $\beta 1$ and $\beta 3$ integrins, in a manner mediated by RhoA signaling [63], and downregulates the transmembrane protein CD99 molecule like 2 (CD99L2), which is a member of the Ras homolog family member A (RhoA) proteins responsible for decreasing neutrophil extravasation [64]. Notably, immune cells require approximately 40 minutes to travel through the basal membrane but only 2 minutes to pass through the endothelium.

Perspectives regarding various cell compartments must be viewed in the context of their cell turnover rate.

Cell turnover

A 70 kg human has an estimated 30 trillion cells (30, 000, 000, 000, 000) [65], with a turnover rate of $0.33 \pm 0.02 \times 10^{12}$ (330 \pm 20 billion) cells d^{-1} , which is equal to approximately 4 million cells s^{-1} , although cell lifespan markedly varies by type and tissue [66]. Approximately 86% of total cell number and turnover consists of blood cells (65% erythrocytes, 18% neutrophils, 12% gastrointestinal epithelial cells, 2.2% lymphocytes, 1% skin cells, 0.5% monocytes, and 0.1% endothelial and lung cells). Additionally, $\sim 38 \pm 10$ trillion bacteria reside in the colon. The neutrophil turnover rate, according to an average of two estimates (bone marrow and the circulating pool) is approximately $6 \pm 1 \times 10^{10}$ cells d^{-1} ; therefore, ~ 60 billion cells (60, 000, 000, 000 cells) are produced every 24 hours. In contrast, CTCs travel very inefficiently, because only 0.2% become metastatic [43]; therefore, the immune system is highly effective in attenuating 99.8% of CTCs in the bloodstream [39].

An incompletely understood aspect of metastases is the heterogeneity of cancers and metastases, including micro-metastases (**Supplement, part 4, Heterogeneity**).

Other important variables include senescence, dormancy, and reawakening from dormancy. The interplay between dormancy and reawakening not only increases cell plasticity but also increases cell heterogeneity. No one variable can distinguish which cell derives from which intermediate stage of senescence, dormancy, or reawakening, and why.

Plant biology has demonstrated that senescence, dormancy, and reawakening are fundamental physiological processes in a strategy for survival in unfavorable environmental conditions. This principle also governs metastasis, because dormancy occurs only under special circumstances with varying durations between nidation, colonization, and reawakening.

Dormancy

The dormancy concept was described in 1867 by Charles Moore (1821–1870), who stated that a “*residual fragment of the original disease should remain quiescent for years*” [67]. In 1948, the heterogeneity in short- versus long relapse-free intervals (e.g., periods of months in gastric and colon carcinoma, approximately 1 year in kidney or tongue carcinoma, and longer periods of quiescence in melanoma and breast cancer) was reported by Rupert Allan Willis (1898–1980) [68].

Geoffrey Hadfield (1889–1968) examined the high variability in the interval between cancer surgery and the appearance of relapsed cancer and coined the term “dormant cancer cell.” He stated, “*When the interval is prolonged to six years or more it seems impossible to escape the conclusion that the cells of the dormant growth are in a state of temporary mitotic arrest, no matter how long the period may be*” [69]. He further used dormancy “to describe

malignant cells which, although remaining alive in the tissues for relatively long periods, show no evidence of multiplication during this time, yet retain all their former and vigorous capacity to multiply." According to Hadfield, dormant cells were located near the tumor's surgical site within the scar, in poorly vascularized mature collagenous connective tissue with relative anoxia or in regional lymph nodes. He assumed that mitotic arrest could be induced by anoxia and that reactivation occurs after oxygen becomes available again (through re-vascularization or inflammation).

Cells in non-proliferating stages can be in quiescence, dormancy, or senescence [70]. Senescent cells are metabolically active but non-proliferative [71].

Quiescence (or latency) (Latin: *quietus*, at rest) is a reversible resting state involving cell division and growth that are repressed under an unsuitable microenvironment but can be reactivated under favorable conditions [72, 73]. An example from botany is the removal of cellular water in plants through the accumulation of protective molecules and formation of intracellular glasses; after rehydration, and in the presence of suitable temperature, light, and oxygen, the plants resume metabolism and germinate [74].

Dormancy (Latin: *dormire*, to sleep) is defined as a reversible state of metabolic activity with reversible proliferation arrest occurring in the G0 or G1 phase of the cell cycle (arrested growth), which can be reactivated under proper conditions in the presence of a necessary specific trigger [75-77]. Quiescent cells have been proposed to be in G0 stage, whereas dormancy would constitute a deeper cell cycle arrest [74], and cells arrested in G1 phase are often quiescent [78, 79], thus potentially explaining why the terms quiescent and dormant are frequently used interchangeably.

Dormancy, a reversible state of diminished metabolic activity, has been observed in viruses, bacteria, fungi, protists, worms, insects, crustaceans, amphibians, fish, birds, plants, and mammals. Dormancy is assumed to have contributed to the emergence of life on Earth, by not only ensuring the biodiversity of life but also decreasing the probability of extinction under limited resource conditions by providing reserve growth potential [80, 81]. A long time ago, it was stated "*Dormancy of the seed during development is so general that it may almost be taken for granted*" [82]. However, dormancy can occur at primary tumors as well as at distant sites of metastasis [83, 84].

Senescence (Latin: *senescere*, to grow old) is defined as terminal growth arrest that leads to death [85]; however, re-entry into a proliferative stage after p53 and p16 inactivation has been reported and termed reversible senescence [86, 87]. The G2-arrested quiescence in *Drosophila* neural stem cells has been reported as a reversible cell cycle arrest in the G2 phase [88].

Senescence differs from dormancy in that senescent cells are believed to undergo irreversible growth arrest associated with senescence-associated β -galactosidase (SA β -gal) [89] and SA- β -gal accumulation [90], both of which are induced by suppressor cyclin-dependent kinase inhibitor 2A (p16, p16INK4a) [91], induction of human chromosome 7, or segments of an *in vitro* established human fibroblast line (SUSM-1) [92]. Lysosomal galactosidase beta 1 (GLB1) [93] encodes an SA β -gal, an extrinsic peripheral membrane protein, that serves as an elastin receptor [94] in senescent cells.

The period from the presence of dormant cancer cells and cell complexes/satellites in the stroma to the emergence from dormancy with metastatic progress has been termed metastatic cancer dormancy [76]. In breast cancer, long latencies of 10-15 years between treatment and relapse, even in node-negative patients, are frequently seen [95, 96]. Long latencies are also seen in node-negative early breast cancer, which increases in dependency of Her2/neu, triple negativity, and estrogen receptor positive (ER+) cohorts [97]. More broadly, dormancy should be considered a normal phenomenon rather than a pathological condition.

Cluster of differentiation 154 (CD154), which is expressed on CD4+ T-cells, CD8+ T-cells, macrophages, natural killer (NK) cells, mast cells, platelets, endothelial cells, and epithelial cells, binds CD40+ T cells, thus forming cluster of differentiation 40 (CD40). Signaling and crosstalk result in CD40 activation and initiation of the senescence-associated secretory

phenotype (SASP) in non-small-cell lung cancer [98]. Notably, senescent cells secrete inflammatory cytokines plus extracellular matrix degrading proteins participating in the remodeling of the extracellular matrix.

Dormant and quiescent cells have been suggested to re-enter the cell cycle and proliferate [78]. Dormancy of occult cancer cells is believed to indicate metastatic potential. “Chemotherapy is not effective in purging bone marrow even in chemo-responsive patients” [99]. Combining high dose chemotherapy with autologous bone marrow transplantation has revealed effective cancer cell elimination, although combinations of various antibodies have not demonstrated enhanced effectiveness [100]. Importantly, most malignant cells and their complexes are in different stages after traveling to distant sites [101–103], thus potentially explaining their relative susceptibility to chemotherapy.

The final step between dormancy and reawakening in metastatic cancer is the exit from quiescence into cell-cycle re-entry, in a process often described as “metastatic reawakening” or dormant cell reactivation. In the literature, this transition is frequently associated with a shift in signaling balance away from dormancy programs, such as p38, and toward pro-growth extracellular signal-regulated kinase (ERK) signaling, thus allowing disseminated tumor cells to proliferate again.

Dormant disseminated tumor cells can persist in a non-proliferative state for years, held in check by signals from the tumor niche, immune surveillance, and extracellular matrix cues. When these constraints are lifted, the cells can re-enter the cell cycle, adapt to the new tissue environment, and progress to metastatic growth. Mechanistically, this process can be explained by dormancy maintenance due to release-from-dormancy signals, cell-cycle re-entry, clonal expansion, and detectable metastatic relapse [104–106].

Currently, dormancy is differentiated into angiogenic [107], immunomediated [108–111], and cellular dormancy, and proliferation is balanced against cell death [112]. Furthermore, dormancy is now known to result from decreased proliferation and not increased apoptosis [113]. This non-proliferative arrest is both reversible and resistant to multimodal cancer therapy.

Dormancy is associated with protein kinase C gamma gene (PRKCG) signaling and increased stromal remodeling [114], as well as the (ERK)(MAPK)/p38(SAPK) activity ratio [115], because the tumor suppressor p38 induces G0/G1 arrest and dormancy [116–119].

Single cancer cells are usually dormant, specific tissue environments favoring ongoing growth and nidation [120, 121]. In such dormant cells, chemotherapy is ineffective [122]. M2 (pro-tumorigenic) macrophages can induce dormancy by increasing angiostatin [123] and by inhibiting neovascularization in cancer, thus resulting in dormancy [124]. Notably, aspirin can upregulate uPAR in human colon cancer [125], and inhibition of uPAR, β 1-integrins, FAK, or eGFR, alone or in combination, can result in dormancy *in vivo* [126].

Reversal from dormancy to fast growing cancer has been observed in various epithelial cancers [127–129]. Reawakening from dormancy is a natural process involving altered stromal cues, decreased dormancy-inducing factors such as secreted protein, transforming growth factor beta2 (TGF β 2) in some niches, restored ERK activity, and integrin/FAK signaling, all of which promote proliferation.

No precise reactivation sequence for dormancy awakening exists because disruption of homeostasis must first occur. An increase in the ERK/p38 MAPK activity ratio with a shift from p38^{HIGH}/ERK^{LOW} dormancy to ERK^{HIGH}/p38^{LOW} drives re-proliferation [76, 115]. Next, because of angiogenesis induction [130], even the fibronectin production in the cytoskeleton can result in awakening [131].

Inflammation [132] and chemotherapy also induce awakening [133–135]. Awakening can be triggered by chemotherapy NET induction [134]. A recent paper has attracted attention by reporting that *Rous* sarcoma virus infection promotes breast cancer cell awakening [136].

Cortisol, epinephrine, norepinephrine, and serotonin activate neutrophils; subsequently, inflammation increases via S100A8 and S100A9, thus altering the distribution of lipids, which accumulate in neutrophils, and leading to reactivation of dormant cells [137]. Because cyclooxygenase (COX) itself can result in awakening, COX2 inhibitors can prevent reactivation

[138]. During dormancy, the signaling pathways of phosphoinositide 3-kinase (PI3K)-AKT and mitogen-activated protein kinase (MAPK), together with RAS–MEK–ERK, are suppressed [139, 140]. Cancer cells themselves can induce PI3K together with autophagy induction by EGFR phosphorylation, AKT inhibition and by inducing Cyclin D1 [139].

Bone stromal cells secrete the TGF- β family member bone morphogenetic protein 7 (BMP7), which, in a BMP receptor 2 (BMPR2) dependent manner, activates p38 MAPK followed by the cell cycle inhibitor p21, and the metastasis suppressor gene N-myc downstream-regulated gene 1 (NDRG1) with cell cycle arrest [141]. Withdrawal of BMP7 restarts cell growth, whereas application of BMP7 suppresses growth, thus explaining why the interplay of BMP7–BMPR2–p38–NDRG1 signaling directly influences dormancy versus awakening, and that why senescence is not irreversible (as previously assumed). Even inactivation of the tumor repressor p53 reverses senescence in fibroblasts [86].

TGF β 2 Smad1 signaling induces the metastasis suppressor DEC2 and BMP7 [141]. CAFs have been shown to secrete CXCL1 with downregulation of DEC2 promoting awakening of dormant cancer cells [142]. CXCL12 release by hepatic stellate cells (HSCs) promote through CXCR4 to exit quiescence and induce cell growth [143]. CXCL9 keeps dormancy stable [144], as does CXCL10/CXCR3 signaling [145], whereas its inhibition results in awakening. Dormancy can be maintained by TGF β through Smad complexes increasing p27 and p21 [146]. Smad4 is essential for transnuclear Smad2/3 transportation and is also a tumor suppressor; notably, Smad4 knockdown reverses p27 activation and growth repression in epithelial cancer cells [147].

Although inactivation of the oncogene MYC results in a dormant state, its reactivation results in awakening [105], as do AP-1 and NF- κ B [148, 149]. Matrix metalloproteinase 9 (MMP9) and neutrophil elastase released by NETs induce α 3 β 1 signaling and awakening of dormant cancer cells [150]. Reoxygenation also results in expression of the E6 and E7 oncogene (E6/7), awakening, and proliferation [151]. E6/7 often result in deregulation of the transcription factor FOXO3 [30, 152].

FOXO3 keeps cells in dormancy via p12 and p27 [153], and PI3K/AKT signaling suppresses FOXO3a promoting cell growth [154]. FOXO3 is an inhibitor of the mammalian target of rapamycin complex 1 or mechanistic target of rapamycin complex 1 (mTORC) with activation of AKT [155]. Suppression of mTORC activity results in cell cycle arrest, including proteomic changes, whereas removal of mTOR inhibitors re-establishes cancer cell growth [156, 157]. Activation of transcription factor 6 alpha (ATF6 α) upregulates the GTPase Ras homolog enriched in brain (Rheb), a critical AKT-independent mTOR signaling inducer [140]; ATF6 α -Rheb-mTOR signaling enhances dormant cell survival *in vivo*, whereas deletion of mTOR in hematopoietic stem cells and progenitor cells (HSPCs) results in a loss of quiescence and increased proliferation [158]. Further information on dormancy is provided in the Supplement (**Supplement, part 5, Dormancy**). The interplay between inflammation and immune evasion with induction of a pro-metastatic microenvironment is important.

Chronic inflammation

Inflammation is a primary defense mechanism to eliminate harm and maintain homeostasis. Many cell types are involved, including fibroblasts and immunocompetent cells, such as antigen presenting dendritic cells (DCs), cytotoxic CD8+ killer T-cells, which require antigen recognition via MHC, natural killer T-cells (NK), which adapt rapidly without antigen specify, together with the coordinating CD4+ T-helper cells (TH), with various subsets Th1, Th2, Th17 and suppressing CD4+ regulatory T-cells (TReg), and mast cells, monocytes, macrophages, platelets, and recruited neutrophils.

In chronic inflammation homeostasis is disrupted, inducing fibrosis and remodeling *through which the normal healthy state become a pro-tumorigenic and pro-metastatic milieu*.

In earlier publications, we discussed ongoing chronic inflammation in detail [16, 17, 30–34], including TGF β , decreased cell-cell-contact by CAM 120/80 (E-cadherin),

and stimulated nuclear factor kappa-light-chain-enhancer of activated B-cells (NF- κ B), phosphatidylinositol 3-kinase (PI3K), with signaling disruption of metalloproteinases (MMPs), zinc finger protein SNAI1 (Snail), Forkhead box protein (FOXO3), CXCL12) and CXCR4 crosstalk. These interactions result in a persistent increase in chronic inflammation through plasminogen activator inhibitor-1 (PAI1), rapamycin complex 1 (mTORC1), reactive oxygen species (ROS), cyclin-dependent kinase 2 (ck2), yes-protein (YAP), and fatty acid desaturase 2 (FADS2, ω -6-desaturase (D6D)), with consequent effects on plasticity; microRNA-21 (miR21) triggered signaling increase in protein 300 (p300, p300-CBP coactivator family), specificity protein 1 (SP1), activator protein 1 (AP1), cytoplasmic complex of Smad3, E2F4/5 and D-prostanoid (DP1) (E2FA4/5), retinoblastoma-like protein 1 (p107, RBL1) and an imbalance of fibronectin, decorin, vimentin, periostin (POSTN), Sox and cytokines, such as interleukin 1 beta (IL-1 β), IL-6, IL8, interleukin 33 (IL33), ROS, CXC CC, interferon gamma (IFN γ), TNF α , alpha-smooth muscle actin (α SMAD).

These factors are each relevant, because their induction occurs at both distant sites and at the primary tumor. Furthermore, the activation of the NF- κ B metabolism [32] is complex. In addition, eicosanoid metabolism [33] has complicated effects on cytochrome P450 isoforms (CYP), cyclooxygenase metabolism, and arachidonate lipoxygenase activity (ALOX), thus leading to the induction of various prostaglandins, prostacyclins, thromboxanes, and leukotrienes. Further information on the effects of chronic inflammation on metastasis signaling and crosstalk is provided in the Supplement (**Supplement, part 6, Chronic inflammation**).

Chronic inflammation, which induces fibrosis and remodeling, further increases not only heterogeneity but also activation of TACs, including signaling and crosstalk. The roles of TACs in metastasis have recently been reviewed [39]. TACs comprise heterogeneous cell populations, including neutrophils, macrophages, and platelets, many of which have been implicated in key steps of the metastatic cascade. TACs are necessary for metastasis regarding neutrophils, TANs, and NETs including elastase, TAMs (M2) together with mesothelin and inhibin. TAPs and elastase are further discussed in the Supplement (**Supplement, part 7, Tumor-associated cells**). Direct or indirect suppression of the immune system results in immune evasion, an important mechanism during metastasis.

Immune evasion

Immune evasion occurs at various levels. Currently, successful organ transplantation is known to depend on genetic compatibility between the donor and host via the major histocompatibility complex (MHC), which also determines cancer transplantation. Furthermore, understanding of the roles of the MHC in cancer is important, because immunosuppression enables cancer growth.

The clearance of cancer cells at distant sites occurs not only via the immune system but also independently at the endothelium by released nitric oxide *in vivo* [159]. Homeostasis is observed because NO derived from cancer cells can also have pro-tumorigenic effects [160]. The anti-tumorigenic immunoglobulin M has been found to increase metastasis in an experimental model [161].

Lamina propria macrophages express high levels of 25F9 (a marker for certain subpopulations of macrophages), MHC class II molecules, and CD74 (MHC class II-associated invariant chain) [162]. Cancer cells and CAFs downregulate MHC-1 class molecules, thus leading to immune evasion [163–165]. MHC-class recognition by cells influences the immune response. NK cells recognize MHC-I through specific receptors preventing them from elimination [166]. CAFs have relatively high mobility (via p130CAS, Src, Crk, RAC, and lamellipodia) but low proliferative ability [167].

High SMAD3, independently of TGF β , recruits CAFs in lung adenocarcinoma. CAFs in turn increase MMPs [168] and downregulate MHC class I-restricted T-cells (CD8+ T-cells), which kill cancer cells [165]. TReg cells are also increased by CAFs [169], and CCL2 increases macrophage suppression [170].

Epithelial carcinomas rich in the endothelial apoptosis inducer Fas ligand (FasL) are associated with few CD8+ T-cells and a variety of regulatory T-cells. FasL inhibition results in tumor suppression [171]. Early B-cell factor 1 (EBF1) is important for B-cell differentiation in B-lymphocytes [172] and can initiate Cox-subunit 412 (COX4I2) transcription in CAFs, thereby promoting M2 macrophage activation and T-cell suppression in CRC [173]. Furthermore, EBF-1 binds CXCL12, Ccl9, and POSTN [174].

IL-10 producing regulatory B-cells (Bregs) [175] make up approximately 10% of B-lymphocytes [176] and regulate anticancer T-cell immunity; therefore, decreasing B-lymphocytes is a potential immunotherapy approach in cancer [177]. CD24^{high}CD27⁺ B cells make up a high percentage of tumor-associated B cells in CRC tumors [178]. Decreasing peripheral CD19⁺CD24^{high}CD27⁺ B lymphocytes in patients with gastric cancer treated with chemotherapy has been found to improve progression free survival [179]. CAFs induce chemokine (C-C motif) ligand 2 (CCL2) with monocyte recruitment and differentiation to mesenchymal stromal cells or myeloid-derived-suppressor cells, thereby suppressing the immune system and promoting angiogenesis [180–182]. CCL2 induces Smad3 Protein- and p42/44 mitogen-activated pProtein kinase (MAPK) signaling increases breast cancer motility [183]. CAFs modify M2-type macrophages, T_{Reg} cells, and myeloid-derived suppressor cells (MDSCs), thereby enhancing immune evasion [184, 185]. In parallel, ongoing chronic inflammation decreases host immunity and the anticancer T-cell response [186]. T cells and B cells, which largely direct the anti-tumor immune response, are notably diminished in number in metastases (only approximately 17%, in comparison to primary breast cancer, whereas the loss of immune activation is approximately 30%) [187].

Eliminating CD8+ T cells in cancer decreases survival [188], whereas the interaction of CD4+ plus CD8+ T-cells increases survival in esophageal cancer [189]. The regulation of CD8+ T-cell replication is increased by antigen presenting DCs [190]. However, various DCs exist and may have both anti- and pro-tumor effects. More details regarding immune evasion during PMNs have been provided in prior publications [39]. Details regarding immune suppression and evasion during metastasis are provided in the Supplement (**Supplement, part 8, Immune evasion**). The complex signaling and crosstalk of chronic inflammation, TACs, with immune evasion induce fibronectin, CXCL12, and K19, as previously reviewed in detail [39]. In cytoskeletal remodeling, gelsolin is important in enabling cancer cells to evade the immune system.

Gelsolin

Gelsolin is a calcium-regulated actin depolymerizing protein involved in regulation of the cytoskeleton [191–193]. Gelsolin inhibits apoptosis and is cancer suppressive [194], and it is downregulated in cancer [195–198]. Gelsolin induces fibroblast and epithelial cell motility. TGFβ induces expression gelsolin, which in turn leads to the conversion of a migratory, stress-fiber-rich phenotype to a cortical actin-rich spheroidal state [199]. Simultaneously, biochemical stiffness and immune evasion decrease. Increased gelsolin results in atypical EMT from an elongated active cancer cell phenotype to a spherical non-active phenotype, which is considered a metastatic dormancy stage and therefore is not vulnerable to immune surveillance.

Another induced secreted small peptide is granulin with its precursors.

Granulin

Granulin and its progranulin form promote migration in breast cancer [200], and increase the H. pylori-induced proliferative activity and migration seen in gastric epithelium [201], in ovarian cancer with its CAFs [202], pancreatic cancer [203], gastric cancer [204], and CRC [205, 206]. Granulin increases migration of the highly suppressive subpopulation of CCR8+ T_{Regs} in bone [207].

Cancer cells actively secrete K19, which prevents CXCL12 from protecting against immune attack [208]. K19 mRNA can be used to identify micro-metastasis in lymph nodes in patients with breast cancer [209]. K19 knockout decreases proliferation, whereas K19,

together with Granulin, POSTN, fibronectin, and CXCL12, increases cancer cell proliferation [210]. Furthermore, K19 increases cell migration in pancreatic cancer via Wnt/ β -catenin [211], although it inhibits cell invasiveness of primary breast cancer [212]. K19 directly promotes cancer cell survival, invasion, and angiogenesis, thus resulting in hepatocellular carcinoma (HCC) progression with poor clinical outcomes [213–215]. Another glycosylated protein important during metastasis signaling and crosstalk is POSTN.

Periostin (POSTN)

POSTN (formerly known as osteoblast-specific factor 2) [216] is a 90 kDa glycosylated protein [217] with several isoforms [218]. This protein plays important roles in epithelial cancers, such as those of the breast [219], prostate [220], lung [221], esophagus [222, 223], stomach [219], ovary [219], head and neck [224], prostate [225], colon [225], colorectum with liver metastasis [225], and others [226]. POSTN is increasingly detected in lymph node, liver, bone, and lung metastases.

The anti-fibrotic agent irfenidone inhibits pancreatic cancer desmoplasia; deposition of POSTN, fibronectin, COL1; and lymph node and liver metastases [227]. In bone, POSTN binds bone morphogenetic protein-1 (BMP-1), which in turn cleaves the LOX precursor propeptide [228]. Osteoblast-induced POSTN is elevated in bone metastases from prostate cancer [229], lung cancer [230], and breast cancer [231–234]. POSTN serves as a surrogate marker for bone metastases in breast cancer [235].

In the liver, POSTN is upregulated in CRC liver metastasis, induces COL1 and fibronectin via the TGF β receptor, independently of Smad2/3 activation with LOX activation in HSCs promoting fibrosis [236, 237]. HSC-derived POSTN induces TGF β in CRC cells through integrin/FAK/ERK/STAT3 and Smad, and its levels correlate with fibrotic features as well as TGF β signaling in CRC liver metastases. Decreased POSTN results in decreased HSC activation and fewer liver metastases [238].

CAFs secrete EVs with activated LOX inducing remodeling and EMT through FAK/paxillin/YAP, interacting with POSTN, fibronectin, and bone morphogenetic protein-1 [239]. CAF EVs activate lung fibroblasts and promote matrix remodeling and POSTN release, together with increased fibronectin, LOX and MMP-9, increases in FAP, α -SMA and Ki67 participating in the creation of a metastatic niche in the lung [240]. POSTN promotes fibronectin expression/secretion and extracellular matrix deposition [241] and modulates myofibroblast differentiation via the integrin β 1/RhoA pathway and fibronectin synthesis [242]. POSTN-positive CAFs activate integrin-FAK/Src-vascular endothelial-cadherin (VE-cadherin) in lymphatic endothelial cells with enhanced metastatic dissemination [243]. Extracellular POSTN mediates fibronectin synthesis via integrin β 1, FAK, and JNK [244], and directly binds fibronectin [217]. The membrane-bound mucin-like glycoprotein podoplanin (PDPN) also induces POSTN expression in fibroblasts and CAFs. More detailed information on PDPN is provided in the Supplement (**Supplement, part 9, Podoplanin (PDPN)**). The remodeling of the tumor microenvironment induced by chronic inflammation increases heterogeneity via cell transition plasticity.

Cell transition plasticity

Another principle to help understand metastases is cell transition plasticity, which is essential for maintaining homeostasis and inducing cell and tissue regeneration, as well as for life. Plasticity is defined as reversible changes in phenotype, functional identity, or differentiation status without alteration of the genome.

The high deformability (plasticity) of cancer cells correlates with the progression of the transformed phenotype from a nontumorigenic cell into a tumorigenic, metastatic cell [245].

Nearly 80 years ago, Conrad Hal Waddington (1905–1975) published the book “*The Strategy of the Genesis*,” which has provided the basis for epigenetics [246]. He described a paradigm for how hierarchical sequential terminal differentiation of cells leads to specialized cells within the development of an embryo from an egg. This paradigm was later modified by Sir John Bertrand Gurdon (1933–2025), on the basis of nuclear transplantation

and consequent formation of differentiated intestinal cells [247]. Shinya Yamanaka (1962) introduced transcription factors for development, and demonstrated that the differentiation of fibroblasts in mice, which was believed to be terminal at the time, could be reverted to a pluripotent stem cell state [248].

This field gave rise to epigenetics, which, along with Waddington's concept of the epigenetic concept led to a persistent importance of the role of epigenetics in disease. Currently, increased cell plasticity is known to not only result from EMT and MET, but also to be enhanced by MMT and pericyte-fibroblast transition (PFT), both of which are representative of mesenchymal-mesenchymal plasticity (MMP), endothelial-mesenchymal transition (EndMT), or mesothelial-mesenchymal transition (MesoMT).

Primary mesenchymal cells can induce E-cadherin activation with re-expression of apical-basal polarity, thereby inducing EMT [249]. Consequently, EMT with activation of TGF β , NT-3, sonic hedgehog, and α 5 β 1 integrin occurs. Transfection of metastatic cells or normal embryonic fibroblasts with the E-cadherin gene has been found to convert normal cells into metastatic invasive cancer cells. Currently, this transdifferentiation is known to be a normal biological process that explains how hepatocytes morph into pancreatic ductal cells [250], how white adipocytes turn into brown adipocytes [251], and how endothelial cells morph into vascular smooth muscle cells [252].

EndMT was first discovered in the study of embryology in heart development [253], in microvessels [254], and in broader *in vivo* and *in vitro* studies in embryology [255]. Even cardiomyocytes can induce transdifferentiation from endothelial cells to cardiac muscle cells [256]. Shear stress can result in a phenotypic change from endothelial to epithelioid [257]. In injured vascular endothelium, bone marrow, monocytes morph into endothelial progenitor cells [258]. Therefore, why EndMT correlates with fibrosis-associated disease, ossification [259–262], cancer [259], malformation [263], and atherosclerosis [264] is currently understood. EndMT is a key link between chronic inflammation and endothelial dysfunction, and an early event in breast cancer metastasis, together with NO deficiency [265]. CAFs can be derived from the endothelium by EndMT [266].

In patients receiving peritoneal dialysis, mesothelial cells undergo MMT, a specific type of EMT, to a myofibroblast-like phenotype; HGF, TGF β , Interleukin-1 β , Vimentin, and fibronectin facilitate this process, thus resulting in extracellular matrix production and fibrosis [267–271]. These findings have been observed both *in vitro* and *in vivo* [272]. The phenomenon is associated with upregulation of thrombospondin-1 (TSP1), collagen-13 (COL13), and gremlin-1 (GREM1). It results in a decrease in epithelial markers such as E-cadherin and cytokeratin, and the induction of mesenchymal markers such as Snail, N-cadherin, fibronectin, collagen I, α -smooth-muscle actin (α -SMA), and fibroblast specific protein-1 (FSP-1).

Mesothelial-to-mesenchymal transition (MMT) is a source of CAFs in peritoneal metastasis [273]. This process can be inhibited by PPAR- γ agonists or TGF β inhibitors [274, 275]. LOXL2 triggered by chronic inflammation-induced TGF β , which promotes EMT, and inhibition of LOXL2 to prevent EMT [276] and thus MMT.

Pericytes (stellate cells) can differentiate into various cells including osteoblasts, phagocytes, adipocytes, and fibroblasts [277, 278]. In fibroblasts, matrix stiffness, together with YAP activation, induces PFT of vascular pericytes with conversion in fibroblasts followed by migration away from the vasculature to matrix stiffness. More details regarding plasticity can be found in the Supplement (**Supplement, part 10, Cell transition plasticity**).

CAFs and metastasis-associated fibroblasts (MAFs)

CAF/MAF differentiation in MMT plays a key role in peritoneal metastasis [279]. In mesothelial cells, MMT is an important source of MAFs and peritoneal metastasis in CRC [273]. Based on their diverse cellular origins MAFs have been classified into myofibroblastic MAF populations; growth factor and inflammatory gene-expressing MAF populations; and portal fibroblast/mesothelial MAF populations, according to a modified CAF single-cell RNA sequencing signature [280]. These findings explain why MAFs show dynamically changing transcriptome profiles during metastasis [281].

MAFs drive not only carcinogenesis but also extracellular remodeling in metastatic epithelial cancers [282, 283]. *In vitro* studies have indicated that CRC-induced peritoneal metastasis originates from MAFs with high levels of IGFBP2 inducing CD38 plus immunosuppression by extracellular adenosine [284]. Application of these findings to available clinical data has revealed that MAFs are associated with poor prognosis. MAFs proliferate and migrate more than metastatic epithelial breast cancer cells [285]. In liver metastasis, these processes are promoted by PDGF, hyaluronic acid, and HGF [286].

In contrast to CAFs, MAFs express CD38 [287] and secrete higher levels of insulin-like growth factor-binding protein 2 (IGFBP2). Furthermore, CXCL12 and MAFs enhance breast cancer growth and metastasis more than CAFs alone *in vivo* [288]. IGFBP2 is immunosuppressive and stimulates IGF1R signaling. Therefore, colony formation of cancer cells is increased by MAFs, together with migration and invasion, and is more potent than that induced by CAFs alone.

MAFs are not only triggered by CAFs but also are induced by EVs [289–291], resident fibroblasts at distant sites [293–297], omental fibroblasts [298], HSCs [299], mesenchymal stem cells (MSCs) [300, 301], mesothelial cells (MCs) [273, 302], endothelial cells [259, 303], stromal cells derived from primary tumors [295], bone-marrow derived MSCs (BM-MSCs) [304], adipocytes [305], and even pericytes [306].

CAFs have very high plasticity [307]. Although CXCL10, CCL8, and metalloproteinase 3 (MMP-3) are secreted predominantly by CAFs, MAFs secrete higher levels of IGFBP2, CXCL12, and CXCL2 [287]. More detailed information regarding CAF-MAF signaling and crosstalk can be found in the Supplement (**Supplement, part 11, CAFs and metastasis-associated fibroblasts**).

One undervalued pro-metastatic and pro-tumorigenic approach is direct or indirect immune escape. In this regard, another example immune evasion escape strategy in cancer involves sialic shielding. Pancreatic cancer cells cloak themselves with sialic acid: integrin $\alpha 3 \beta 1$, which is composed of ITGA3 and ITGB1 subunits, bind on the receptor Siglec-10, followed by inhibitory signaling to TAMs [308]. Siglec-10 was identified, cloned, and characterized in 2001 [309, 310]. Siglec-10 and cluster of differentiation 24 (CD24) suppress the immune response after tissue damage [311]. The cell adhesion molecule CD24 is expressed on epithelial cancers, such as those of the breast, lung, pancreas, prostate, colorectum, kidney, and ovary [312, 313]. This type of immune escape through pro-tumorigenic macrophage (M2) suppression has been demonstrated with CD24 and Siglec10 crosstalk in breast and ovarian cancers [314]. Siglec-10 is associated with poor survival in HCC [315], and inhibiting Siglec-10 in HCC M2s results in immune escape [315, 316]. Such shielding of tumors has also been shown in leukemia cells [317].

On the basis of careful observations by biochemists and pathologists dating back to Virchow, many beliefs were declared as “hallmarks” or “breakthroughs” in cancer and metastasis. Apoptosis provides an example. Cancers have long been known to have elevated frequencies of apoptosis [318]. Cancer cells are short (not long)-lived as also observed decades ago by the surgeon Alexis Carrel (1873–1944) and the pathologist Albert Fischer (1891–1956) [319, 320]. Therefore, the notion that resistance or avoidance of apoptosis is a hallmark of cancer is incorrect. The consequence of unstoppable cell proliferation is, in fact, an increased rate of apoptosis. For creation of tissue, cells must exit proliferation by entering G0 stage, but as more cells proliferate, and more cells die, the G0 cell ratio decreases, thus resulting in decreased differentiation and structure, and increased cancer proliferation rates, necrosis rates, and apoptotic index values as cancer cells increasingly die [321]. Therefore, Bcl-2 is not elevated in aggressive breast or colon cancers. Interestingly, in this regard, Francis Peyton Rous (1879–1970), who was awarded the Nobel Prize in 1966 for the discovery of Rous sarcoma virus in 1911 [322], rejected the belief that cancer could be a genetic disease [323, 324]. Consequently, others wrongly judged Rous to be stubborn [325]. In our view, Rous was not stubbornly ignoring facts; instead, the authors who judged him a century later refused to accept the reality that he had observed.

Essential predisposing conditions for metastases

The formation of three metastatic niches, as discussed above, creates essential conditions for metastases. Each metastatic niche is formed through multiple factors, including chronic inflammation, remodeling, signaling, and crosstalk, as summarized below.

Metastatic niche 1 (MN-1) (FIGURE 1)

Metastatic niche 1 (MN-1) develops from the pre-metastatic niches (PMNs) [39]. Cancer satellites extravasate after traveling and nidate at the capillary bed after transendothelial migration, when de-coating into constituent parts occurs with EMT, MET, MMP, recruitment of immunocompetent cells, senescence, and dormancy (**Fig. 1**).

Metastatic niche 2 (MN-2) (FIGURE 2)

The transformation of metastatic niche 1 (MN-1) to metastatic niche 2 (MN-2) is induced by chronic inflammation, fibrosis, and remodeling (via lysyl oxidase). Pro-tumorigenic TACs, EVs, and chemokine ligand 2 (CLL2) induce immune suppression. Granulin, periostin, fibronectin, CXCL12, and K19 increase motility, and the migration of non-dormant CAFs and cancer cells (**Fig. 2**). Further recruitment of fibroblasts induces LOX, which is followed by collagen crosslinking through oxidation of lysine residues, increased stiffness, and decreased elasticity. LOX also induces FAK, p130(cas)/crk/DOCK180 formation, which in turn increases lamellipodia/motility. Previously recruited macrophages, platelets, and neutrophils lead to pro-tumorigenic TACs with TAMs (M2), TAPs, and TANs. CAFs secrete EVs and CCL2, which in turn lead to the transformation of monocytes into MSCs, as well as immune suppression via decreased CD8+ T-cells and increased CD4+ TReg cells. These changes in the microenvironment result in consistent increases in granulosa, periostin, CXCL12, fibronectin, and K19, thus further increasing motility and promoting cancer cell migration.

Metastatic niche 3 (MN-3) (FIGURE 3)

Metastatic niche 3 (MN-3) finally develops in which cell plasticity increases, active elongated cancer cells are present, and the newly developed MAFs re-trigger dormancy. Current anticancer therapies such as surgery trauma, chemotherapy, radiotherapy, immune therapy, and ongoing inflammation induce dormancy awakening, gelsolin with atypical EMT to spherical non-active cancer cells, followed by dormancy once more with increased heterogeneity, leading to metastatic cancer satellites and to immune suppression (**Fig. 3**). Therefore, the predisposing conditions for metastases are fulfilled: (1) metastatic cancer cells and (2) MAFs migrate along gradients; (3) metastatic cancer cells surrounded by MAFs are shielded from the immune system and consequently migrate to distant sites; (4) CXCL12 and K19 coat metastatic cancer cells; (5) platelets surround metastatic cancer cells, and (6) MAFs enable effective metastasis; (7) NETs shield metastatic cancer cells, and (8) MAFs, in parallel with ongoing dormancy and re-awakening, provide the basis for later metastasis. Distant metastatic niches create a high degree of heterogeneity of CAFs, MAFs, dormant and awakened cancer cells that progress to either metastatic cancer satellites that meet the predisposing conditions for metastases, or lead to dormancy.

Summary

It is an integral part of human existence and science to try to find answers to open questions, and if these be extremely complex, to simplify. Here, the human mind is affected by a bias which prefers simple explanations to complex phenomena although many variables might better explain real world outcomes or events. Such biases distort reasoning when it comes to the complexities of metastases [326]. Theories of cancer and

metastasis development, including the somatic mutation theory, the clonal evolution theory, the epigenetic theory, the immunologic theory, the Warburg paradigm, and the stem cell cancer theory, have each essentially been simplifications, although the perspectives gained from immunology and stem cell science are important and complex. We are aware that some in retrospect may state that we combined parts of such into Epistemology of the origin of cancer. Here, we assume not defending against such arguments.

To us, providing a logical explanation for creating progress with primary cancer patient care as our goal was, and remains the primary focus, although not all questions had been answered, and new questions always come up in answering others. Our intent is not to question the origin of hereditary or the 5% of cancers caused by mutation, or the success of the 10% of cancers, such as leukemias, lymphomas, myelomas, or melanomas. During the past few decades, knowledge from genetics/epigenetics/proteomics has substantially increased. Here, disciplines have increased our knowledge in signaling and crosstalk in cancer biology. What is necessary in cancer science is to explain why and how some 80% of epithelial cancers occur, as genetic, epigenetic, and proteomic analyses alone may be insufficient to explain their initiation, progression, and metastatic behavior without considering epithelial physiology, tissue architecture, and stromal interactions. Although many genes, epigenetic changes, proteins, and molecular pathways contribute to epithelial carcinogenesis, no single molecular event or universal set of molecular events has been shown to account for the full initiation, progression, and metastatic behavior of human epithelial cancers.

Cancer and metastasis are essentially states of disruption of homeostasis with complex signaling and crosstalk. Addressing fundamental questions in carcinogenesis and metastasis provide a much more nuanced, yet logical explanation: epithelial cancer develops predominantly from (1) a pathogenic stimulus, (2) chronic inflammation, (3) fibrosis and remodeling, and a (4) PCN detail [16, 17]. As mentioned, this sequence of events was later independently demonstrated in an animal model [36]. (5) Chronic stress escape strategy (CSES) lead by EMT into CAFs. (6) Finally, CAFs, aided by MET, can differentiate into cancer cells, and epithelial markers facilitate their integration into the epithelium [37]. The credit of the concept, that fibroblasts are the initial precursors of cancer, goe back to Virchow 168 years ago [38].

Metastasis is a complex phenomenon. Ongoing disruption of homeostasis with signaling and crosstalk transforms the PCN to PMNs during carcinogenesis [39]. PMN-1 involves p130 (cas)/crk/DOCK180 formation and consequent formation of lamellipodia, which enable cell mobility. As CAFs release fibronectin, CXCL12, and K19, the PMN-1 is transformed into PMN-2, with the transformation of anti-tumorigenic into pro-tumorigenic TAPs, TAMs (M2), and TANs. Persistent signaling and crosstalk induce immune evasion, and the transition of PMN-2 into PMN-3. Eight cancer satellites serve as prerequisites for intravasation/traveling: (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; (4) CXCL12 and K19 coat cancer cells; (5) platelets surround cancer cells and (6) CAFs; and (7) NETs shield cancer cells and (8) CAFs [39]. Therefore, the PMNs create the conditions for the extravasation of heterogeneous cells and components.

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. At this stage, metastatic colonization is observable under the microscope.

The dissemination of metastatic cancer satellites is the major starting point for metastasis. Metastatic cancer cell heterogeneity is markedly increased by plasticity, as well as by the ongoing interplay between dormancy and reawakening; the transformation of CAFs to MAFs; and elongated active, and spherical inactive cancer cells. The metastatic niches are important basic steps in metastatic cell dormancy with secondary cancers with time delays. This metastatic dormancy can be seen in accordance with CD154/D40 signaling and crosstalk, CD40L transgene resulting in CD40 overexpression, initiating the SASP in non-small-cell lung cancer [98]. In brief, the high heterogeneity in cancer with its PMNs [39],

and metastasis with its more complex metastatic niches (MNs), substantially increases heterogeneity. As discussed, this complexity might be a major reason why unidirectional views remain favored paradigms for cancer and metastasis despite incompletely explaining the disease. The vast heterogeneity may even limit universal rules, although in summary, the primary focus was, and remains, to develop a logical framework for advancing cancer research with improved patient care as the central goal.

We acknowledge that our work does not answer all questions and new questions will arise. Opening new book chapters reveal limitations on various levels, e.g. in regard to translational model(s) and/or an indirect proof as a logical method (if the opposite is impossible or leads to a contradiction). The analyzed knowledge pieced together here was provided by independent hundreds of separate studies in animal and human cancers. Despite the independent demonstration of the sequence of events of Part I [36], so far no single experiment has validated the full framework. Clinically we do not have a method to determine in which niche a cancer patient is in, or have verified potential additional blood or imaging markers in this regard. We also do not have measurable criteria or markers to identify or differentiate boundaries between dormancy, quiescence, and senescence in clinical samples. Exemplary, real-time dynamics in cell plasticity will be a challenge, as there can be intermediate states [327] and e.g., EMT cancer cells very rapidly can polarize toward a mesenchymal or epithelial phenotype [328]. Therefore, the vast heterogeneous interplay of adaptable changes in protein, subcellular and cellular compartments can range from micro-to-milliseconds, minutes, days, weeks, months or even years, because nature is never constant as assumed in models but consistently dynamic to maintain homeostasis. Nevertheless, a brief overview of implications to minimize or prevent metastasis were provided earlier [39].

Conclusions

Epithelial cancer and distant metastasis involve highly heterogeneous cancer cells, CAFs, MAFs, cell components, signaling, and crosstalk, which remain incompletely understood in the context of how their interactions promote disease. Regarding primary cancer and metastasis, each cell type is clinically recognized through histopathology, immunohistochemistry, and molecular biology, but their collective effects remain to be parsed.

The fourth unanswered question in cancer biology concerns the essential conditions that permit metastasis to develop, including the role of tumor and microenvironmental heterogeneity. The ongoing disruption of homeostasis lies at the core of development of metastatic niches (MNs) and their sequential progression to metastases as illustrated in our Graphical Highlights and figures (**Figs. 1 to 3**).

The essential predisposing conditions for metastases are as follows:

Cancer satellites from PMNs result in the first metastatic niche (MN-1), with nidation at the capillary bed, transendothelial migration, de-coating into constituent parts, recruitment of immunocompetent cells, cell transition via EMT and MET, and dormancy (**Fig. 1**).

Metastatic niche 1 (MN-1) transforms into metastatic niche 2 (MN-2) with chronic inflammation, fibrosis and remodeling, TAMs, EVs, CLL2 with immune suppression, and increased motility of non-dormant cancer cells and CAFs along with granulins, periostin, fibronectin, CXCL12, and K19. (**Fig. 2**).

Metastatic niche 3 (MN-3) is characterized by elevated heterogeneity due to plasticity, with development of MAFs, elongated active and spherical non-active cancer cells, and finally to heterogeneous metastatic cancer satellites with Trojan horses that facilitate immune evasion, and the interplay of dormancy and reawakening, alongside specific sequences metastasize alone or in combination at the distant site (**Fig. 3**): (1) metastatic cancer cells and (2) MAFs migrate along gradients; (3) metastatic cancer cells surrounded by MAFs are shielded from the immune system and consequently migrate to distant sites; (4) CXCL12

and K19 coat metastatic cancer cells; (5) platelets surround metastatic cancer cells and (6) MAFs, thus enabling effective metastasis; and (7) NETs shield metastatic cancer cells and (8) MAFs, in parallel with ongoing dormancy and re-awakening, thus forming the basis for later metastases.

Plasticity is not only a major reason for the high heterogeneity in cancer and metastasis early during carcinogenesis [39] but also has been demonstrated to emerge early during colorectal carcinogenesis and to be driven by fibroblasts, which direct the timing and the location of plasticity [329]. Furthermore, inhibition of transcription factor EB (TFEB) through binding to 14-3-3 σ , a frequently inactive regulatory p53 tumor suppression protein in CRC, promotes MET and inhibits autophagy in CRC [330]. The H1R antagonist, cetirizine, suppresses CAF-mediated remodeling and plasticity through signaling and crosstalk via COL1A1, COL3A1, fibronectin, FN1, heparan sulfate proteoglycan 2 (HSPG2), and TGF β in breast cancer cells (4T1). These findings suggest that the microenvironment regulates cell transition and metastasis [331]. CAF activation can be disrupted by photodynamic therapy, via CAF-mediated IGF1-IGF1R signaling and upregulation of RGS2, which in turn suppresses cancer progression [332].

Anticancer therapy, cancer surgery, and inflammation can favor the creation of MNs, thus explaining the frequent clinical observation of early appearing or later increased metastasis after a primary tumor undergoes surgery. This aspect also explains the paradoxical findings of a mixed response to anticancer therapy, and observations of metastasis with various mixed aggressive epithelial carcinomas with various rates and compositions of mesenchymal cell types and with various phenotypes. Furthermore, it sheds light on why highly metastatic epithelial cancers frequently show a highly mixed response in terms of the primary tumor versus metastasis in the lymph nodes or liver, lung, bones, or other locations.

The observations in metastatic cancers explain why Isaiah Josh Fidler (1936–2020), a grandfather of metastasis research, wisely concluded in 1979 that “*the search for a property uniform to all metastatic cells may be unproductive*” [333], although “*multiple cancer drugs have received “breakthrough therapy” designation, none to date have been safer, more effective, or more novel than drugs without this designation*” [2]. Metastasis rates in epithelial cancers have not changed during the past century [2]. Perhaps it is time to recall the words of Henry Louis Mencken (1880–1956), who published an article in 1917, and later a book [334, 335], stating: “*Explanations exist; they have existed for all time; there is always a well-known solution to every human problem—neat, plausible, and wrong.*”

Simplification of models of metastasis to better understand complex cascades in a highly controlled environment has yielded only limited insights in vitro, because the in vivo situation is much more complex. In this regard, in 1877, Theodor Billroth (1829–1894) stated: “*Nature is rarely dealt with in a simple ‘either-or’ way; it’s all much more complicated than it first appears, and that we would like*” [English translation] [336]. However, biology in humans is dynamic and never in a steady state. Various cancer models are excellent for identifying biochemical signaling or crosstalk. Otherwise, such have their limitations, e.g., having different aggressiveness, not capturing the interplay of dormancy and its awakening, individual steps during metastasis, or the complexity of participating cells, compartments, or the immune system, or their heterogeneity. Oversimplification might be a major reason for the currently limited understanding of how to better approach and treat epithelial cancers and their metastases.

As illustrated in our Graphical Highlights and the figures, the suggested sequence of steps leading to distant metastatic niches is summarized in **Figs. 1–3**, illustrating the genesis of high heterogeneity of CAFs, MAFs, dormant and awakened cancer cells which progress to metastatic cancer satellites, and these aid in fulfilling the predisposing conditions for metastases. Additionally, this heterogeneity is deciphered to explain why no single anticancer targeted therapy approach can be successful, and a much more nuanced and differentiated anticancer therapy approach is necessary, as partially described earlier [39].

Abbreviations

12-HETE 12-hydroxyeicosatetraenoic acid; **20-HETE** 20-hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,14Z)-20-hydroxyicoso-5, 8,11, 14-tetraenoic acid; $\alpha_{IIb}\beta_3$ platelet glycoprotein IIb/IIIa integrin; **α SMA** alpha smooth muscle actin; **ActA** Activin A; **Adgre1** adhesion G protein-coupled receptor E1, F4/80; **AKT** protein kinase B; **ALOX** arachidonate lipoxygenase; **ANGPTL1** angiopoietin-related protein 1; **AP-1** activator protein 1; **Arg1** arginase 1; **bFGF** basic fibroblast growth factor; **BLBCs** basal-like breast cancers; **BMP-1** bone morphogenetic protein-1; **CAF** cancer-associated fibroblast; **CCC** cholangiocellular carcinoma; **CCL2** chemokine (C-C motif) ligand 2; **CD31** cluster of differentiation 31, platelet endothelial cell adhesion molecule, PECAM-1; **CD40** cluster of differentiation 40; **CD44** cluster of differentiation 44 cell-surface glycoprotein; **CD47** cluster of differentiation 47, integrin associated protein (IAP); **CD62E** ligand for E-selectin;

CD99 cluster of differentiation 99, MIC2, single-chain type-1 glycoprotein; **CD99L2** transmembrane protein CD99 molecule like 2; **CD154** cluster of differentiation 154; **CD202B** cluster of differentiation 202B, TEK tyrosine kinase (TIE2); **CD206** cluster of differentiation 206, mannose receptor; **CD340** cluster of differentiation 340, human epidermal growth factor receptor 2 (HER2/neu), erythroblastic oncogene B receptor tyrosine-protein kinase erbB-2 (ErbB2); **cdk** cyclin-dependent kinase; **C/EBP β** CCAAT/enhancer-binding protein beta; **ck2** cyclin-dependent kinase 2; **CLEC-2** C-type lectin-like receptor 2; **Clec4f** C-type lectin domain family 4 member F;

LL2 chemokine ligand 2; **COL1A1** collagen type I; **COL11A1** collagen type XI alpha I chain; **COL13** collagen-13; **Cox** cyclooxygenase; **Cox-1** cyclooxygenase 1; **Cox-2** cyclooxygenase 2; **CRC** colorectal cancer; **crk** adapter molecule (p38); **CSES** chronic stress escape strategy; **CSF1R** colony stimulating factor 1 receptor; **CTC** circulating tumor cells; **CUP** cancer of unknown primary; **CYP*** cytochrome P450 isoforms; **CXC** CC chemokine receptors; **CXCR4** C-X-C motif of chemokine receptor 4; **CXCL1** C-X-C motif chemokine 1, GRO- α ; **CXCL4** C-X-C motif chemokine4, platelet factor 4 (PF4); **CXCL5** C-X-C motif chemokine 5, Epithelial-derived neutrophil-activating protein 78, ENA-78; **CXCL7** C-X-C motif chemokine 7, platelet basic protein; **CXCL10** C-X-C motif chemokine ligand 10; **CXCL12** C-X-C motif chemokine 12, stromal cell-derived factor 1 (SDF-1), pre-B cell growth-stimulating factor (PBSF); **DCs** antigen presenting dendritic cells; **DmiR** dormancy-associated miR; **DOCK180** dedicator of cytokinesis; **E2F4/5** cytoplasmic complex of Smad3, retinoblastoma-like protein 1 (P107, RBL1), E2F4/5 and D-prostanoid (DP1); **EBV** Epstein-Barr virus; **EBF1** early B-cell factor 1; **E-cadherin** CAM 120/80 or epithelial cadherin, cadherin-1, epithelial cadherin; **EMT** epithelial-mesenchymal transition; **EMP1** epithelial membrane protein 1; **ENA-78** Epithelial-derived neutrophil-activating protein 78, C-X-C motif chemokine 5; **EndMT** endothelial-mesenchymal transition; **ENO2** enolase 2; **EpCAM** epithelial cell adhesion molecule, cluster of differentiation 326, CD326); **ER** estrogen receptor; **ErbB2** erythroblastic oncogene B receptor tyrosine-protein kinase erbB-2, human epidermal growth factor receptor 2 (HER2/neu), cluster of differentiation 340 (CD340); **ERK** extracellular signal-regulated kinase; **ESAM** endothelial cell adhesion molecule; **ESCC** esophageal squamous cell carcinoma; **ET-B** endothelin receptor type B (ETB1); **EV** extravesicular vesicle; **F4/80** adhesion G protein-coupled receptor E1, Adgre1; **FADS2** fatty acid desaturase 2, ω -6-desaturase (D6D); **FAK** focal adhesion kinase; **FAP** fibroblast activation protein; **Fas** ligand (FasL); **FGF21** fibroblast growth factor 21; **FGFR4** fibroblast growth factor (FGF) receptor 4; **FOXO3** Forkhead box protein; **FSP1** fibroblast-specific protein 1, S100 calcium binding protein A4, S100A4; **GARP** glycoprotein A repetitions predominant; **gas6** growth arrest-specific protein 6; **G-CSF** granulocyte colony-stimulating factor; **GhHSP24.7** Gossypium hirsutum (Gh) heat shock protein (HSP) with approximate molecular weight 24.7 in kilodaltons (kDa); **GLB1** galactosidase beta 1; **GPCR** adhesion G protein-coupled receptor (high-mobility group box 1, HMGB1); **GREM1** gremlin-1; **GRO- α** C-X-C motif chemokine 1, CXCL1; **HB-EGF** heparin-binding epidermal growth factor; **HCC** hepatocellular carcinoma; **HER2/neu** human epidermal growth factor receptor 2; **HGF**

hepatocyte growth factor; **HMGB1** adhesion G protein-coupled receptor (high-mobility group box 1, GPCR); **HSCs** hepatic stellate cells; **Hsp47** heat shock protein 47; **IAP** integrin associated protein, cluster of differentiation 47 (CD47); **IFN γ** interferon gamma; **IL-1 β** interleukin 1 beta; **IL-4** interleukin 4; **IL-6** interleukin 6; **IL-8** interleukin 8 (CXCL8); **IL-26** interleukin 26; **IL-27** interleukin 27; **IL-33** interleukin 33; **ICAM-1** intercellular adhesion molecule 1, CD54; **INHBA** inhibin subunit beta A; **IGFBP1** insulin-like growth factor binding protein 1; **ITGA11** integrin α 11 β 1; **ITGB4** integrin β 4; **JAX** Jackson laboratory; **JNK** c-Jun NH2-terminal kinase; **KCs** resident Kupffer cells, KC1 (CD45⁺ F4/80⁺ CD11b^{int} TIM-4⁺ ESAM⁻) and KC2 (CD45⁺ F4/80⁺ CD11b^{int} TIM-4⁺ ESAM⁺); **K19** keratin 19; **LMP1** latent membrane protein 1; **LOX** lysyl oxidase; **LPS** lipopolysaccharide; **LSEC** liver sinusoidal endothelial cell; **LTBP1** latent transforming growth factor beta-binding protein 1; **LTs** leukotrienes; **LYVE1** lymphatic vessel endothelial hyaluronan receptor 1; **MAGE-A3/6** melanoma-associated antigens A3 and A6; **MCs** mesothelial cells; **MDSCs** myeloid-derived suppressor cells; **MesoMT** mesothelial-mesenchymal transition; **MET** mesenchymal-epithelial transition; **MFAP5** microfibril associated protein 5; **MHC** major histocompatibility complex; **MIIP** migration and invasion inhibitory protein (IIP45); **miR21** microRNA-21; **MMP** mesenchymal-mesenchymal plasticity; **MMPs** metalloproteinases; **MMP-3** metalloproteinase 3; **MMP-9** metalloproteinase 9; **MMP-12** metalloproteinase 12, macrophage elastase; **MMT** mesothelial-mesenchymal transition; **MNs** metastatic niches; **MN-1** metastatic niche 1; **MN-2** metastatic niche 2; **MN-3** metastatic niche 3; **MSCs** mesenchymal stem cells; **MSLN** mesothelin, CAK1 antigen, pre-pro-megakaryocyte-potentiating factor; **mTORC1** rapamycin complex 1; **NASH** non-alcoholic steatohepatitis; **NCCCT** normal cell to cancer cell transition; **NETs** neutrophil extracellular traps; **NF- κ B** nuclear factor kappa-light-chain-enhancer of activated B cells; **NK** natural killer T-cells; **NPY** neuropeptide Y; **NPY1R** neuropeptide Y (NPY) receptor Y1; **NUPR1** nuclear stress protein nuclear protein 1, p8; **NURF** nucleosome remodeling factor; **OL** oral leukoplakia; **OSCC** oral squamous cell carcinoma; **p16** cyclin-dependent kinase inhibitor 2A (p16, p16INK4a); **p21** cyclin-dependent kinase inhibitor 1, alternatively p21^{Waf1}; **p38** MAPK mitogen-activated protein kinase; **p53** tumor protein p53; **p107** retinoblastoma-like protein 1, RBL1; **p130(cas)** breast cancer anti-estrogen resistance protein 1, BCAR1; **p300** protein 300, p300-CBP coactivator family; **PAI1** plasminogen activator inhibitor-1; **PBSF** pre-B cell growth-stimulating factor, C-X-C motif chemokine 12 (CXCL12), stromal cell-derived factor 1 (SDF-1); **PCN** precancerous niche; **PDGF- β** platelet-derived growth factor beta; **PDPN** podoplanin; **PECAM-1** platelet endothelial cell adhesion molecule, CD31, Cluster of differentiation 31; **PF4** platelet factor 4 (C-X-C motif chemokine4, CXCL4); **PFT** pericyte-fibroblast transition; **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; **PGF2** prostaglandin F2 alpha, (Z)-7-[(1R,2R,3R,5S)-3, 5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid; **PKR-1** prokineticin receptor; **PPG2** 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; **PGI2** prostaglandin I2, prostacyclin I2, (5Z)-5-[(3aR,4R,5R,6aS)-5-hydroxy-4-[(E,3S)-3-hydroxyoct-1-enyl]-3, 3a,4, 5,6, 6a-hexahydrocyclopenta [b]furan-2-ylidene]pentanoic acid; **PI3K** phosphatidylinositol 3-kinase; **PLT-Exos** exosomes derived from platelets; **PMN** premetastatic niche; **PMN-1** pre-metastatic niche 1; **PMN-2** pre-metastatic niche 2; **PMN-3** pre-metastatic niche 3; **POSTN** periostin, former osteoblast-specific factor 2; **PPAR γ** peroxisome proliferator-activated receptor γ ; **PRKCG** protein kinase C gamma gene; **PTPase** protein tyrosine phosphatase; **RANKL** receptor activator of NF- κ B ligand; **RhoA** Ras homolog family member A; **RIGS** radioimmune-guided surgery; **ROS** reactive oxygen species; **S1P** sphingosine-1-phosphate; **S100A4** S100 calcium binding protein A4, fibroblast-specific protein 1, FSP1; **S100A8** calcium-binding protein A8; **S100A9** calcium-binding protein A9 (S100A9), migration inhibitory factor-related protein 14 (MRP14); **SA β -gal** senescence-associated β -galactosidase; **SASP** senescence-associated secretory phenotype; **SCLC** small

cell lung cancer; **SCRNA seq** single-cell RNA sequencing; **SDF-1** stromal cell-derived factor 1, C-X-C motif chemokine 12 (CXCL12), pre-B cell growth-stimulating factor (PBSF); **se-cad** soluble CAM 120/80 (E-cadherin); **SERPINE1** Serpin Family E Member 1; **S-Gal** beta-galactosidase-related protein; **Shp2** Src-homology 2 domain-containing tyrosine phosphatase 2; **SIRT1** mammalian sirtuin 1; **Snail** zinc finger protein SNAI1; **SOX** [sex-determining region Y (Sry) box-containing] transcription factor family; **SP1** specificity protein 1; **SPARC** secreted protein acidic and rich in cysteine, osteonectin; **SPP1** phosphoprotein 1; **STAT3** transcription factor activator protein 3; **TAC** tumor-associated cell; **TAGLN** transgelin; **TAM** tumor-associated macrophage; **TAN** tumor-associated neutrophil; **TAP** tumor-associated platelet; **TENS** tumor-entrained neutrophils; **TGFβ** transforming growth factor beta; **TGFβ2** secreted protein, transforming growth factor beta2; **TH** T-helper cells, with various subsets Th1, Th2, Th17 and suppressing CD4+ regulatory T-cells (TReg); **TIE2** TEK tyrosine kinase, cluster of differentiation 202B (CD202B); **Tim4** T-cell immunoglobulin and mucin domain containing 4; **TLR9** Toll-like receptor 9; **TMT1A** thiol methyltransferase 1A; **TNFα** tumor necrosis factor alpha; **TReg** suppressing CD4+ regulatory T-cells; **TSP1** 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; **VCAM-1** vascular cell adhesion protein 1, cluster of differentiation 106 (CD106); **VE-cadherin** vascular endothelial-cadherin; **VEGF** vascular endothelial growth factor; **VIRMA** vir-like m6A methyltransferase-associated protein (KIAA1429); **YAP** yes-protein.

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