Supplemental Material

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

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Part 1: Capillaries

Interaction of the endothelium with platelets is necessary for the arrest of cancer cells in the lungs [1], but cancer cells need not undergo transendothelial migration in distant organs, because they can attach to the endothelium and proliferate in the vessels [2]. C-X-C motif of chemokine receptor 4 (CXCR4) increases cancer cell adhesion both *in vitro* and *in vivo* through b1 integrin [3].

Cell-cell communication in the endothelium occurs through various redundancies, such as nucleotide signaling (purinergic signaling) (e.g., by adenosine and ATP) [4], purinergic receptors for adenosine (P1) and adenosine di- and tri-phosphate (P2), and Ca^{2+}-dependent tight junctions [5–7], ion channels for ionic current and membrane potential modulation [8], gap junctions between the endothelium and pericytes [9] for the exchange of ions and small molecules [10], gap junctions composed of various connexins [11], basic fibroblast growth factor (bFGF) [12], platelet-derived growth factor beta (PDGF) [13], heparin-binding epidermal growth factor (HB-EGF) [14], and adhesion molecules, e.g., selectins, integrins, intercellular adhesion molecule 1 (ICAM-1, CD54), vascular cell adhesion protein 1 (VCAM-1, CD106), PECAM-1, Caveolin-1, cadherins, CD99, and CD47 [15–21].

Part 2: Soluble selectins

Soluble factors are important. Soluble E-selectin in the human triple negative cluster of CD44+/high breast cancer cell line (MDA231-TGL) mediates endothelial adhesion, FAK phosphorylation, and endothelial permeabilization (for which ICAM-1 is necessary) [22]. E-, L-, and P-selectin negative animals exhibit diminished lung metastases, and treatment with a pan-selectin inhibitor decreases migration and proliferation [23]. Sialylated glycosphingolipids (gangliosides) on breast cancer cells are E-selectin ligands [24] as well as CD44 variant isoforms [25]. Serum soluble E-selectin levels are elevated in liver metastatic breast cancer [26], and in lymphatic and metastatic breast cancer [27].

Levels of soluble P-, L-, and E-selectins are higher in human CRC than in healthy controls. The highest levels of sP-selectin have been measured in liver metastatic CRC (as compared

to non-metastatic CRC), and the highest sL- and sE-selectin levels have been found in lymph node metastatic CRC [28, 29].

Sialyl Lewis(x) (sLe(x)) is expressed on activated endothelial cells. A ligand for E selectin (CD62E) and elevated sLe(x) levels are found in low metastatic CRC [30]. Elevated levels of the adhesion molecules E-selectin, ICAM-1 and VCAM-1 are also found in metastatic gastric cancer [31].

Soluble CAM 120/80 (E-cadherin) (sE-cad) are markedly elevated in metastatic small cell lung cancer (SCLC), and non-small cell lung cancer (NSCLC) [32]. Moreover, soluble (s)P-selectin and sE-selectin levels do not differ among various benign lung diseases, although they are elevated in metastatic squamous lung cancer but not in adenocarcinoma. The significance of such changes are unclear at present as only sE-selectin has been independently found to have prognostic value [33].

Part 3: Pericytes

Heterogeneous phagocytic, contractile, and pluripotential pericytes [34, 35] were first reported by Charles-Marie Benjamin Rouget (1824–1904) in 1873 as Rouget cells [36, 37]. The term pericyte was coined in 1923, on the basis of the location of cells around endothelial cells [38]. Pericytes derive from the mesoderm and also directly from endothelial cells. Pericytes have pluripotent stem cell [39–41] and fibroblast-like [42] characteristics, and are located in the capillary endothelium, embedded in the basement membrane [43]. Their prevalence is highest in the central nervous system [34]. An estimated 90% of the endothelial surface is covered with pericytes [44]. Brain capillary endothelial cells have numerous tight junctions [45].

Pericytes in capillaries are elongated and have slender processes whereas in postcapillary venules they are stubby and have thick and short radial processes [43]. Furthermore, pericytes have contractile functions, e.g., to decrease capillary diameter (perfusion regulation) [46]. Pericytes have PDGF-β receptors [43], which are also found on endothelial cells and on fibroblasts [47].

In the liver, pericytes are called hepatic stellate cells (HSCs), and are located between sinusoidal endothelial cells and hepatocytes (parenchymal) [48]. Their nomenclature is

somewhat confusing because it has changed over time. Carl von Kupffer first described these cells in 1876 (Kupffer Sternzelle) [49]. Toshito Ito, in 1952, reported perisinusoidal cells as fat storing cells [50], which were named Ito cells. Kenjiro Wake described them as HSCs [51] and, in 1974, described vitamin A storage in pericytes [52]. The main term in use since 1996 has been HSCs [53].

Kupffer cells are highly abundant sinusoidal liver macrophages. Currently, two functionally different liver resident Kupffer cells are known: KC1 ($CD45^+$ $F4/80^+$ $CD11b^{Int}$ TIM-4^+ $ESAM^-$) in as many as 85%, and KC2 ($CD45^+$ $F4/80^+$ $CD11b^{Int}$ TIM-4^+ $ESAM^+$) in as many as 15% [54, 55]. Both types have high expression of C-type lectin domain family 4-member F (Clec4f), T-cell immunoglobulin and mucin domain containing 4 (Tim4), colony stimulating factor 1 receptor (CSF1R), and adhesion G protein-coupled receptor E1 (F4/80, Adgre1), and have low CD11b expression.

KC1 has low cluster of differentiation 206 (CD206, mannose receptor) expression and is negative for endothelial cell-selective adhesion molecule (ESAM−), whereas KC2 shows high CD206 expression and ESAM positivity (ESAM+). KC2 expresses more liver sinusoidal endothelial cell (LSEC)-like genes, including Esam, Pecam1, CD206, and lymphatic vessel endothelial hyaluronan receptor 1 (Lyve1).

Kupffer cells typically defend against cancer cells [35]. Loss of the non-receptor protein tyrosine phosphatase (PTPase) Src-homology 2 domain-containing tyrosine phosphatase 2 (Shp2) in Kupffer cells and hepatocytes leads to pro-tumorigenicity [56]. Anti-cancer-Kupffer cells can be transformed into pro-tumorigenic Kupffer cells through stimulation with interferon gamma or muramyl peptides [54].

Part 4: Heterogeneity

Metastases are more heterogeneous than primary cancers [57–60]. CAFs and CTCs are also more heterogeneous in metastases than within primary tumors [61–65]. The reason for why heterogeneity exists during carcinogenesis has been explained previously [66].

A recent analysis of serous tubal intraepithelial carcinomas revealed multiple heterogeneous cell pools, in accordance with observed epithelial transcriptomic profiles, all of which were associated with chronic inflammation, immunoregulation, remodeled matrix, cell transition induced plasticity, and dormancy [67]. These findings are in line with

a previously proposed paradigm for the development of cancer [11, 66–76], the first cancer cell [66], and the basis for new perspectives on how metastasis arises [77].

The heterogeneous pool of CAFs evolves from fibroblasts, fibrocyte recruitment from the bone marrow, and epithelial cells, which undergo EMT. Consequently, the heterogeneous cell pool of secondary fibroblasts expresses both epithelial and mesenchymal markers, and ultimately differentiates into CAFs. The stromal microenvironment of epithelial cancers is fundamentally different from that of leukemias [78]. Fibroblasts are less abundant in normal kidneys than in the lungs, lymph nodes, or spleen. After renal fibrogenesis, approximately 36% of new fibroblasts come from the local EMT, 14–15% come from the bone marrow, and the rest come from local proliferation [79]. This finding reinforces that fibrogenesis is a local epithelial event. Additionally, fibrogenesis increases as metastasis arises in parallel with carcinogenesis, and eight traveling cancer satellites, including Trojan horses (immune evasion), travel alone or in combination [77].

CAFs express mesenchymal markers [80–93] such as fibroblast activation protein (FAP), alpha smooth muscle actin (αSMA), Vimentin (type III intermediate filament protein), podoplanin (PDPN), collagen type I (COL1A1), microfibril associated protein 5 (MFAP5), collagen type XI alpha I chain (COL11A1), PDGF receptors, secreted protein acidic and rich in cysteine (SPARC), S100 calcium binding protein A4 (S100A4; fibroblast-specific protein 1, FSP1), transgelin (TAGLN), periostin (POSTN), PDPN, and integrin α11β1 (ITGA11).

In summary, the high heterogeneity of the precancerous niche (PCN) and primary tumors in terms of marker expression on CAFs and epithelial cancer cells has been described. Furthermore, this explains, as reported due to ongoing EMT, followed by MET, and reverse EMT during carcinogenesis [66], that CAFs and epithelial cancer cells have both mesenchymal and epithelial markers. Therefore, CAFs also express epithelial cytokeratin markers, and epithelial cancer cells display secondary mesenchymal markers [94]. However, some cell transition processes occur so rapidly that these markers are difficult to observe, and/or the complexity of influencing factors makes characterization difficult.

The heterogeneity of primary epithelial cancers is high as previously explained [66, 77], and the heterogeneity further increases in metastasis. This cannot be defined by measured

rates of maximum speed of travel although cancer cells have varying rates (e.g., breast, 2.4 μ/min; kidney, 4.4 μ/min; and fibrosarcoma, 6.2 μ/min [95].

Other explanations include the adhesiveness of cancer cells [96, 97], which is often associated with in situ calcium deficiency [96, 98, 99]. However, the data are far too heterogeneous to draw firm conclusions.

Cell heterogeneity is broadly increased by micro-metastasis.

Micro-metastasis

Metachronous micrometastases can occur in parallel and after cancer cell growth. The risk of occult cancer in autopsies has been reported to be approximately 2% after 40 years of age and as high as 50% after 80 years of age [100 *reviewed in* 101]. However, this risk decreases after the age of 95 years, according to autopsy studies [102].

Breast cancer has a reported bone metastasis rate as high as 40% [103], which might actually be much greater, given that autopsy investigations have indicated rates as high as 70% [104]. In autopsy studies, microscopically dormant tumors, such as thyroid papillary carcinoma [105] or breast cancer [106], are frequently observed.

However, occult cancer cells are detectable in the bone marrow in people with lung cancer [107, 108] and in the lymph nodes in people with various cancers of the colon [109], rectum [110], lungs [111], and liver [112]. Occult bone marrow cancer cells are present in 32% of pancreatic cancers [113], 30% of gastric cancers [114], 36% of breast cancers [115], 38%–63% of small lung cell cancers [116, 117], 59.7% of NSCLCs [118], and 36% of prostate cancers [119].

In one investigation, 81% occult cancer cells were found in bone marrow aspirates of patients with prostate, breast, colon, or kidney cancers [120]. Use of reverse transcription-PCR assays combined with the highly sensitive electrochemiluminescence automated detection system enhanced detection of systemic metastasis by 32% [121]. As we have stated, metastases occur in parallel with cancer as supported by the observations that even in early breast cancers, the percentage of metastases is 23% [122]. A direct comparison across studies is difficult, because of their use of different analytical techniques.

Growth arrest-specific protein 6 (gas6) is negatively regulated during cell growth [123–126]. Cytokeratin-positive (cytokeratin polypeptide 18, mAb CK2) cell rates have been reported in the bone marrow (occult bone marrow metastasis) in 18.1% of patients with breast cancer and 21.1% of patients with colon cancer. These cells were not found in the bone marrow of patients with no evidence of malignant diseases [127]. The frequency of tumor cell detection varies from 9.5% to 23.3%, depending on the site analyzed and whether unilateral or bilateral bone marrow aspiration is performed. Furthermore, patients with lymph node involvement have the highest incidence of cancer cells in the bone marrow and typically have poor prognosis.

A total of 33% of breast cancer patients with bone marrow micrometastases, compared with 3% of those without micrometastasis, show recurrence within 2 years [128]. In patients with breast cancer, the number of micrometastases increases with cancer stage: 23% in stage I, 38% in stage II, and 50% in stage III. Patients with lymph node negative breast cancer show 27% occult bone marrow cancer cells, in contrast to the 41% in lymph node positive patients [122]. These data have been reproduced [129].

Bone marrow involvement has been reported in 42% (359 of 838) of carcinomas, and micrometastases have been found in 18% of 359 positive biopsies from patients with solid tumors. The high incidence of human epidermal growth factor receptor 2 (HER2/neu) expression observed in micrometastatic breast cancer cells in the bone marrow supports the notion that "*the majority of these cells appear to be in a dormant state of cell growth*" [130].

In 386 bone marrow aspirates from 242 patients with carcinoma, 31% of occult epithelial tumor cells were immunohistochemically positive, whereas 69% were negative. Notably, cytokeratin status did not correlate with TNM stage or even histological grade [131]. However, monoclonal antibody 17-1A (Edrecolomab), targeting the cell-surface glycoprotein epithelial cell adhesion molecule (EpCAM), completely eliminated occult epithelial tumor cells in 40% of mice [132]. Importantly, this rate was not 100%, an important aspect for understanding metastases.

In one study, random bone marrow biopsies from 6 of 28 patients with diagnosed prostate carcinoma (21.4%) revealed bone metastases [133].

Reproducible data on bone marrow biopsies have been confirmed: 22% in early prostate cancer and 34% in metastatic prostate cancer [199]. Higher numbers have been found among 3,150 patients with cancer: 42% in patients with carcinoma, 15% in patients with Hodgkin's lymphoma, 55% in patients with malignant lymphoma, and 75% in patients with myeloma. Moreover, the rate of bone marrow metastases in cancer of unknown primary (CUP) was 82% [134].

Part 5: Dormancy

Cancer cells become dormant after platelet interaction. In a murine model, antibody-induced platelet depletion (by 50%) was found to significantly decrease tumor growth (50%), tumor cell proliferation (44%), and microvessel density (51%) [135].

As defined in the main manuscript, cells in non-proliferating stages can be in quiescence, dormancy, or senescence; senescent cells are metabolically active but non-proliferative. 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; 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; senescence (Latin: senescere, to grow old) is defined as terminal growth arrest that leads to death.

Dormancy has long been observed in plants [136, 137] in which the mitochondrial matrix-located heat shock protein GhHSP24.7 controls mitochondria, which are important for seed germination in a temperature-dependent manner [138]. The dormancy concept of cell survival was incorporated into cancer biology to explain how micrometastatic cells can persist for long periods before being re-activated resulting in metastases [139]. This dormancy was interpreted by Hadfield (1889–1968) as a temporary mitotic arrest and proposed in his Kettle Memorial Lecture in 1954 [140, 141].

Dormancy was experimentally demonstrated in 1959 [142, 143] in rats with intraportally injected liver cancer cells. No cancer was observed after 5 months, but if laparotomy (wound healing) was initiated, all animals showed cancer. Surgery induced manipulation and increased free circulating cancer cells [144].

Incomplete cancer resection, concordant with what is currently known as R1 (microscopically incomplete) or R2 resection (macroscopically incomplete), has long been known to result in higher metastasis rates and early cancer death [145, 146].

Patients with surgically treated cancer show higher rates of CTCs and significantly shorter survival times than patients without surgery [147]. One challenge is that the indirect effects after surgical manipulation can be measured, but occult cells cannot be identified through histology. Modifying the above experiment by massaging the liver has also been found to result in cancer spread, thereby reproducing Fisher's approach [148].

Cancer cell dormancy has been suggested to be reversible by trauma, inflammation, carcinogenic activity, or hormones, or to be inducible by the alkaloid colchicine in mice, in a condition termed stathmokinesis, indicating an interrupted state of meiosis [149]. An association between dormancy and the hormone milieu has further been suggested [150, 151]. Ludford previously demonstrated inhibition of growth and cell cycle arrest by applying a 1:800 to 1:100,000 dilution of colchicine in vitro and in vivo in mice [152].

Irradiation in plants, seeds and crown gall tumors has been shown to result in dormancy [153].

The immune system was initially assumed to control dormancy [154] on the basis of the dormancy of cancer cells and their subsequent reactivation [155]. Long-term persistence of tumor cells in the bone marrow in a dormant state is associated with long-term immunological protection [156], and cytotoxic CD8+ T cells have been found to control malignant lymphoma cells in dormancy in bone marrow and lymph nodes [157, 158]. However, in prostate and breast cancer, immune competence has not been found to correlate with time to recurrence [159, 160].

Dormant micro-metastasis has been demonstrated in gastric cancer [161, 162], and activation of dormant micrometastasis has been observed after surgery [163, 164]. However, occult cancer cells are usually present as single cells, whereas only approximately 7% are present in cell clusters [115]. The median detected frequency of occult metastatic cells, three cytokeratin-positive cells per 2×10^6 bone marrow cells, increases with tumor stage.

In the 1960s, cancer cells were reported not to travel or circulate for prolonged periods [165, 166]. However, carcinoma and sarcoma transplantation experiments revealed that cancer cells can pass through the circulation of the liver, lungs, spleen, and kidneys [167–169 *reviewed in* 170], and can travel much longer than previously assumed [171 *reviewed in* 170]. Cancer cells can immediately pass through the pulmonary circulation (in rabbits and rats); consequently, transpulmonary passage has been suggested to be more frequent than previously believed [167].

In one study, an occult cancer site was detected in 9.2% of 104 primary or recurrent CRC cases [172], and occult lymph node metastasis was observed in approximately 50% of patients with CRC treated with radioimmune-guided surgery with a mouse monoclonal antibody (CC49) [173]. Subsequently, the occult lymph node metastasis rate was 10 of 57 lymph nodes (17.6%) after radioimmune-guided surgery and iodine-125 (^{125}I)-labeled CC49 antibody administration approximately 3 weeks before surgery [111].

Dormancy was demonstrated to be part of avascular tumors, but cancer cells still appeared viable and mitotically active. On the basis of observations of rapid and invasive cancer growth after re-implantation with vascular access, an endothelial trigger was proposed [174–176].

Cancer in isolated perfused organs with endothelial degeneration is associated with fewer metastatic tumor implants [177]. This observation is concordant with the finding that the cell connection with macrophages and their interaction is necessary to stimulate cancer cell extravasation [178].

Metabolic adaptations have been suggested to dictate distal organ-specific metastatic colonization [179]. However, although the metabolic pathways associated with disruption of homeostasis have not been proposed, micrometastasis has been shown to be nonproliferative and to occur in the G0 phase [180]. These findings suggest that micrometastases are typically dormant.

CD40 is highly expressed in epithelial lung, gastric, ovarian, and skin cancer, as well as lymphoma [181]. Hypomethylation silences gene function [182], and some microRNAs (miRs), known as dormancy-associated miRs (DmiRs), function as epigenetic silencers: DmiR miR202 in esophageal squamous cell carcinoma (ESCC) dormancy [183], like DmiR miR-340-5p in hepatocellular carcinoma (HCC) [184], and DmiR-580 and DmiR-

190 in aggressive glioblastoma [185]. Downregulation of DmiRs correlates with switching of cancer cells from dormancy to a rapid growth phenotype, although tumor cell proliferation is not attenuated by DmiR-overexpression. Bv8 regulates DmiR as a downstream target, and granulocyte colony-stimulating factor (G-CSF) is not found in glioblastoma. Therefore, DmiR (i.e., DmiR-580, DmiR-588, and DmiR-190) downregulates bv8 in a manner dependent on G-CSF.

Moreover, silencing of SAβ-gal decreases chronic inflammation and reverses aging [186]. Dormant cancer cells can show senescence-like characteristics, including upregulation of cyclin-dependent kinase inhibitor 1 (p21, $p21^{Waf1}$) or mitogen-activated protein kinase (p38 MAPK) [187]. p21 inhibits the transcription factor cyclin-dependent kinase (cdk), which is activated by tumor protein p53 (p53) [188]. Downregulation of the histone deacetylate mammalian sirtuin 1 (SIRT1) results in cyclin-dependent kinase inhibitor 1 (p21) activation [189]. Dormant cells are associated with SAβ-gal and upregulation of cyclin-dependent kinase inhibitor 2A (p16, $p16^{INK4a}$) [190].

Integrin activation results in the production of fibronectin and insoluble fibrils, decreased p38, and cell proliferation [191]. Furthermore, lipoxygenase components of arachidonic acid metabolism mediate the adhesion response [74, 192, 193], and extracellular glycoproteins, such as fibronectin produced by fibroblasts, promote adhesion to the substrate and fibroblast migration [194]. This finding might explain why the Epstein-Barr virus (EBV) takes a long time to induce cancer: it is encoded primarily by latent membrane protein 1 (LMP1), activates NF-κB and c-Jun NH2-terminal kinase (JNK)/activator protein 1 (AP-1), and leads to chronic inflammatory stimulation of interleukin-6 (IL-6) and interleukin 8 (IL-8) expression. In contrast, it activates the tumor suppressor p38 [195].

The condition of the primary cancer and the distant condition are both important. In an orthotopic breast cancer mouse model, induced stress was not found to have a major effect on the primary cancer; however, a 30-fold-increase in the metastasis rate to the lymph nodes and lungs was directly mediated by β-adrenergic signaling and increased infiltration of CD11b+ F4/80+ macrophages in the primary tumors [196].

M2 macrophages directly induce the premetastatic condition of re-awakening from dormancy (as discussed below for M2 macrophages).

Cortisol, epinephrine, norepinephrine, and serotonin, applied as stress hormones to dormant tumor cells from mice, have been found to activate neutrophils; increase inflammation via calcium-binding protein A8 (S100A8) and calcium-binding protein A9 (S100A9); and alter the distribution of lipids, which accumulate in neutrophils and lead to reactivation of dormant cells [197]. In this regard, eicosanoid metabolism and phospholipids are believed to be involved [74].

Inflammation also triggers immunocompetent cells. Only ~0.02% of injected cancer cells survive [198], whereas most are destroyed by the immune system [199]. Similar findings have also been found to occur after extravasation in animal models [200]. Another reason has been demonstrated through melanoma cell experiments: 95% of single cancer cells remain dormant, whereas this rate in macroscopic tumors is approximately 3% [201]. Therefore, although single cancer cells are usually dormant, specific tissue environments favor ongoing growth and nidation [202, 203]. In such dormant cells, chemotherapy is ineffective [204]. Moreover, even dormant cancer cells can change shape, thus facilitating further immune evasion [205].

Part 6: Chronic inflammation

Ongoing chronic inflammation [11, 68, 71–75] includes activation of TGFβ, a decrease in cell-cell-contact by CAM 120/80 (E-cadherin), stimulation of nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-kB) and phosphatidylinositide 3-kinase (PI3K), signaling disruption of metalloproteinases (MMPs), zinc finger protein SNAI1 (Snail), Forkhead box protein (FOXO3), and CXCL12)/CXCR4 crosstalk. These changes result in a persistent increase in 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), and consequently affect plasticity. MicroRNA-21 (miR21) triggered signaling induces increases 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), and retinoblastoma-like protein 1 (p107, RBL1). Subsequently, imbalances result among fibronectin; decorin; vimentin; POSTN; Sox; and cytokines such as interleukin 1 beta (IL-1β), IL-6, IL8, interleukin 33 (IL33), ROS, CXC CC, interferon gamma (IFNγ), TNFα, and alpha-smooth muscle actin (αSMAD).

Activation of NF-kB metabolism [73] and eicosanoid metabolism [74] involves cytochrome P450 isoforms (CYP), induces 20-hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,14Z)-20-hydroxyicosa-5,8,11,14-tetraenoic acid (20-HETE), and 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 (PPG2). The induction of cyclooxygenase metabolism results in increases in 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 (PGH2), 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 (PGI2), prostaglandin E2, (Z)-7-[(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid (PGE2), prostaglandin D2, (Z)-7-[(1R,2R,5S)-5-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid; (PGD2), prostaglandin F2 alpha, (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid (PGF2), and 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 (TXA2).

Increases in arachidonate lipoxygenase (ALOX) result in the formation of leukotrienes (LTs) and 12-hydroxyeicosatetraenoic acid (12-HETE).

Chronic inflammation increases the numbers of free cancer cells with elevated metastatic potential [206], and can awaken dormant cancer cells by increasing metalloproteinase 9 (MMP-9), laminin cleavage, and integrin α3β1 signaling [207].

Laminins, discovered in 1979, are noncollagenous components of the basal membrane [208, 209] and are associated with cancer [210, 211]. Laminins, heterotrimeric extracellular matrix glycoproteins composed of α, β, and γ polypeptide chains, are found in all basement membranes, and affect cell adhesion and migration [212–214].

Integrins are heterodimeric transmembrane receptors involved in bi-directional cell communication between cells and the ECM. They serve as distinct laminin receptors on the cell surface and mediate adhesion to ECM components [215–217]. Moreover, they appear to be a condition for metastasis.

The laminin receptor integrin α6β4 is overexpressed in NSCLC, and it promotes disease progression and metastasis [218]. In colon cancer, the release of integrin α6β4 by hemidesmosomes activates RhoA, which in turn translocates from the cytosol to the cell membrane, in a manner regulated by cAMP via the formation of lamellae and cell migration [219 *reviewed in* 218].

Furthermore, integrin α6β4 upregulates PI3K, protein kinase B (AKT), and NF-κB [73, 220], in another condition in the metastasis sequence [221].

Transactivation of CXCR4 by IGF-1R through PI3K signaling phosphorylating AKT, independently of the ligand CXCL12, triggers elevated proliferation and metastasis in breast cancer [222]. However, IGF-1R induced CXCR4 transactivation occurs in only metastatic cancer cells and not non-metastatic cells [223].

Platelet glycoprotein IIb/IIIa ($\alpha_{IIb}\beta_3$ integrin) binds fibrinogen and von Willebrand factor, thus supporting platelet activation and the subsequent release of activators (adenosine diphosphate and thromboxane A2) [224–227].

Platelet aggregation was demonstrated to be induced by cancer cells approximately 60 years ago [228, 229], and this induction was later shown to depend on $\alpha_{IIb}\beta_3$ integrin [230]. This finding has been reproduced in leukemia [231] and lung cancer [232]. The compound 12-HETE induces $\alpha_{IIb}\beta_3$ integrin expression on melanoma cells [233]. $\alpha_{IIb}\beta_3$ integrin is expressed not only by megakaryocytes but also by cancer cells [234]. Electron microscopy has indicated heterogeneous $\alpha_{IIb}\beta_3$ integrin expression on melanoma and lung cancer cell surfaces with high concentrations on microspikes and filopodia, as well as within cytoplasmic vesicles. Therefore, $\alpha_{IIb}\beta_3$ integrin is present in melanoma, leukemia, lung cancer, squamous cell carcinoma, cervical cancer, colon cancer, and prostate carcinoma [235 *reviewed in* 334]. In humans, 18α and 8β subunits have been identified.

Fibrosis with remodeling

Chronic inflammation, such as that induced by a virus (HCV), increases C-X-C motif chemokine ligand 10 (CXCL10) [236], which in turn induces CXCR3 in macrophages [237] and promotes fibrosis remodeling by LOX. In contrast, CXCL10 knockout attenuates fibrotic remodeling [238]. CXCL10 from macrophages induces CXCR3 and osteoclast

differentiation, and promotes the formation of osteolytic bone metastases via type I collagen as well as RANKL-mediated osteoclast formation [239].

Fibroblast growth factor (FGF) receptor 4 (FGFR4) is elevated in cancer where it increases Ras-Raf-MAPK and PI3K-AKT signaling, cell migration, EMT [240], and increases CAFs through CXCL10 [241]. Therefore, ongoing chronic inflammation does not occur only at primary tumor sites during carcinogenesis but also occurs through chemokine (C-C motif) ligand 2 (CCL2) induced signaling and crosstalk at distant sites, resulting in fibrosis and remodeling (LOX) [66, 72, 77]. *Therefore, increased LOX directly activates cancer cell dissemination* [242].

Chronic inflammation [29] results in fibrosis and remodeling through LOX, thereby forming a PCN associated with MMP activation [30]. MMPs induce heat-shock protein activity and transcription. For example, knockout of heat shock protein 27 (HSP27) decreases AKT signaling, thus improving prognosis in head and neck cancer [243], but also decreases FGF in breast cancer, resulting in dormancy [244]. High levels of fibroblast growth factor 21 (FGF21) are associated with cancer progression in colon, breast, liver, lung, and thyroid cancers, and downregulate CD8+ cytotoxicity. In contrast, FGF21 deficiency in tumor cells decreases cancer growth and increases tumor-infiltrating T cells [245]. FGF21 expression is diminished in prostate cancer but elevated in benign prostate hyperplasia. FGF21 inhibits prostate cancer cell migration and invasiveness [246]. FGF21 facilitates autophagy in prostate cancer, thereby inhibiting cell proliferation through inhibition of PI3K–AKT–mTOR. Therefore, in prostate cancer, FGF21 has a tumor suppressive function. FGF21 increases osteoclast activity by enhancing peroxisome proliferator-activated receptor γ (PPARγ) activity [247] through insulin-like growth factor binding protein 1 (IGFBP1) and integrin β1 binding, thereby increasing receptor activator of RANKL-stimulated extracellular regulated protein kinase phosphorylation and non-alcoholic steatohepatitis (NASH) nuclear factor of activated T cells 1 activation, and ultimately promotes osteoclast differentiation and decreased bone mineral density [248].

In some cancer types, including breast and pancreatic carcinomas, CAFs are the most prominent stromal cell type [249]. Furthermore, established tumors recruit CAFs and stimulate their own growth, as in liver cancer [250–252].

Within the local tumor microenvironment, CAFs and cancer cells migrate in alignment with the fibronectin and KT19 gradient. Here, CAFs promote directional cancer cell migration by aligning fibronectin [253] and cancer cells can follow a gradient by deformed collagen I [254]. CAFs even align the matrix so that cancer cells can follow [255–257]. Suppression of fibronectin and beta1 integrin activation results in decreased adhesion and diminished prostate cancer [256].

Moreover, CAFs actively induce fibrosis in pulmonary pre-metastasis stage via LOX [258]. Coculturing of normal lung fibroblasts with breast cancer cells results in fibroblast transition to CAFs, dormancy, and resistance to therapy [259].

Part 7: Tumor-associated cells (TACs)

Neutrophils and tumor-associated neutrophils (TANs)

Neutrophils have high concentrations of MMP-9 [260] and induce the release of EGF, TGFβ, and PDGF from the ECM, thereby stimulating cancer cell proliferation [261]. MMP inhibition blocks neutrophils from migrating through the basal membrane in a manner independent of gelatinase B [262].

Ongoing TGFβ simulation results in transition from anti-tumorigenic TANs (N1) to pro-tumorigenic TANs (N2), whereas TGFβ inhibition has opposite effects and results in N2 transition to N1 [263]. Elimination of granulocytes results in cancer inhibition by preventing growth [264].

The transition toward a pro-metastatic milieu can be seen by tumor-entrained neutrophils (TENs), which are activated by G-CSF and CCL2, and accumulate at distant organs before metastasis occurs [265]. TENs appear to act as precursor cells during the metastatic evolution from N1 to N2. TENs have anti-metastatic properties and inhibit cancer cell seeding by inducing apoptosis and hydrogen peroxide (H_2O_2) release. TENs, after cancer cell contact, are directly cytotoxic (in contrast to naïve neutrophils), and they inhibit tumor cell seeding in the lungs by inducing apoptosis.

Neutrophil extracellular traps (NETs)

By forming extracellular web-like structures called NETs, neutrophils expel nuclear DNA together with nuclear histones and granular and cytoplasmic proteins [266–269]. This strategy helps neutrophils eliminate invading microorganisms and is important in carcinogenesis. NETs serve as a prognostic marker and are elevated in precancerous lesions such as oral lichen planus [270], as well as in cancers of the head and neck [271, 272], esophagus [273], bowel [274–277], liver [278], and breast [279].

Neutrophils with high expression of Ly6G and low expression of Ly6C (Ly6G+Ly6C-) form more NETs than so-called classical Ly6GHighLy6CHigh neutrophils and consequently exhibit a pleomorphic necrotic architecture [280]. The number of intravascular neutrophil aggregates correlates with the extent of non-perfused vessels, and the resultant decreased perfusion and necrosis. Such areas have revealed neutrophil and NET infiltration.

NETs are upregulated in gastric cancer [281] and help gastric cancer cells cluster and grow on the peritoneal surface [282]. If NETs are inhibited, apoptosis increases and invasion is inhibited [283]. Intriguingly, NETs in gastric cancer are found predominantly in the omentum [282, 284]. Furthermore, NETs are increased by surgical stress [285]. NETs also bind circulating cancer cells [286], and neutrophil Mac-1/ICAM-1 binding appears to be an early adhesive step in the development of liver metastasis [287].

NETs induce increased plasticity and have been found to promote an aggressive phenotype in gastric cancer, both *in vitro* and *in vivo*, by inducing EMT [288]. This mechanism has also been demonstrated in breast cancer [289].

Furthermore, NETs are important in cancer spread [266, 269]. NETs increase G protein-coupled receptor (high-mobility group box 1, GPCR, HMGB1) adhesion and Toll-like receptor 9 (TLR9) signaling, thereby promoting adhesion, proliferation, migration, and invasion, and facilitating liver metastasis [290]. NETs are found in gastric, liver, and pancreatic cancer [281, 290, 291]. Intravital imaging has revealed cancer cells surrounded by NETs [292].

Induction of GM-CSF results in recruitment of Ly6G+Ly6C+ granulocytes, immature neutrophils that promote migration and metastasis through activation of the Bv8 receptor

prokineticin receptor 1 (PKR-1) [293]. Recombinant GM-CSF not only increases Ly6G+Ly6C+ granulocytes in organ-specific metastatic sites but also enhances metastatic ability.

Through the cellular process of blebbing [294–296], rapid cell membrane protrusions are formed and shed extracellular vesicles, also known as blebs [297, 298]. Blebbing is relevant to cell motility without lamellipodia [299] in amoebae, leukocytes, and many metastatic cancer cells [300]. Blebbing by neutrophils can result in the release of NETs; in this process, termed vital NETosis, where the primary neutrophil remains alive and releases some of its genetic material.

NETs consist of extracellular fibers, granule proteins, and chromatin, are triggered by Toll-like receptors, Fc receptors, and complement receptors, lipopolysaccharide [301, 302].

Elastase and NETs

Elastase activity increases neutrophil and cancer cell adhesion to the vascular endothelium [303]. Human neutrophil released elastase breaks down elastin in the stroma, thus decreasing its elasticity, and triggering time- and dose- dependent endothelial cell damage [304]. Elastase is also released by macrophages (through MMP-12, macrophage elastase) [305], platelets [306], fibroblasts [307], T-cells [308], tumor-associated platelets (TAPs) and NETs [309, 310], TANs [311], stimulated alveolar macrophages in the lungs, and stimulated peritoneal macrophages [312].

Bladder cancer cells secrete elastase [313], and breast cancer cells can acquire elastase from neutrophils [314]. Elastase is elevated in various cancers, such as prostate cancer, lung cancer, breast cancer, ulcerative colitis associated CRC, and metastatic gastric cancer [315]. Inhibition of elastase decreases metastasis rates in breast cancer [316].

Macrophages and tumor-associated macrophages (TAMs)

Activated macrophages express and secrete TGFβ [317, 318]. The macrophage mannose receptor, CD206, is highly expressed in alternatively activated macrophages, which have an anti-inflammatory phenotype. Intriguingly, conformational changes in CD206 induced by muramyl peptides promote the transition of activated (M2-like) TAMs to an antitumor

classically activated macrophage (M1-like phenotype), thereby enhancing innate anti-tumor immunity [319 *reviewed in* 320].

Lipopolysaccharide induces CD206+ macrophage-like cells with pro-inflammatory TNF-α [321]. The eicosanoid metabolism derived anti-inflammatory Maresin-1 [74] transforms the Kupffer cell population and induces an anti-inflammatory and hepatoprotective phenotype [322].

TAMs express arginase 1 (Arg1), and secrete platelet factor 4 (PF4), resulting in polarization of T_{regs}, a subset of helper CD4+ T cells, into TH1-T_{regs}, which suppress antitumor immunity [323].

Pro-tumorigenic M2 macrophages induce pericyte-fibroblast transition (PFT) in HSCs, which is followed by POSTN secretion as well as granulin. Subsequently the depletion of granulin decreases HSC activation and liver metastasis from pancreatic cancer [324].

TAMs express phosphoprotein 1 (SPP1) and, through SPP1-CD44 and CD155-CD226 ligand-receptor interactions, facilitate colonization and proliferation of disseminated tumor cells in lymph nodes in oral squamous cell carcinoma (OSCC) [325].

Endothelin receptor type B (ET-B, ETB1) is upregulated in cancer of the esophagus [326] and breast [327]. Inhibition of stromal ET-B diminishes infiltration by TAMs and suppresses metastasis [328]. ET-B can also be silenced through hypermethylation in colon cancer [329].

Mesothelin and TAMs (M2)

Pro-tumorigenic M2 macrophages (M2) are activated through various signaling and crosstalk pathways, as previously described [77].

The protein mesothelin (MSLN; CAK1 antigen, pre-pro-megakaryocyte-potentiating factor), is expressed on normal mesothelial cells and is upregulated in cancer tissue. It was discovered in 1992 during the isolation of a monoclonal antibody reacting with ovarian cancer cells [330]. MSLN is elevated in mesothelioma and ovarian cancer [330, 331], adenocarcinoma of the pancreas or the stomach; and extrahepatic cholangiocellular carcinoma (CCC) [332]. MSLN induces IL-6/sIL-6R trans-signaling [333], binds MUC16 in ovarian cancer, enabling peritoneal spread [334, 335]; activates NF-κB, protein E,

transcription factor activator protein 3 (STAT3), and induces EGFR-ERK1/2 signaling thereby promoting liver metastasis of triple-negative breast cancer [336]. MSLN binds CD2006 and subsequently promotes pro-tumorigenic M2 macrophages in ovarian cancer [337] and CRC [338].

Inhibin and TAMs (M2)

The inhibin subunit beta A (INHBA) homodimer [339] is part of the TGF-β superfamily. Two subunits form Activin A, which induces TGF-β signaling. It was first reported to be induced by Smad2 [340] but was later also reported to be induced by Smad2/3 [341, 342]. INHBA functions as a tumor suppressor and increases in its expression are associated with decreased cell proliferation and anti-angiogenesis in prostate [343, 344] and gastric [345] cancers. INHBA upregulates the expression of vir-like m6A methyltransferase-associated protein (VIRMA, also called KIAA1429) in OSCC [346]. In addition, INHBA promotes progression in ovarian cancer [347] and is associated with aggressiveness and lymph node metastasis in esophageal cancer [348]. Furthermore, INHBA is associated with progression of pancreatic carcinoma [349], prostate cancer [343] and CRC [350].

INHBA is also overexpressed in gastric cancer and associated with poor survival and increased metastatic spread. The transcription factor CCAAT/enhancer-binding protein beta (C/EBPβ) induces INHBA, resulting in PI3K/AKT/TGFβ activation, M2 macrophage polarization, and cancer progression [351].

These findings explain why radiation-induced inflammation is associated with macrophage polarization toward the M2 phenotype and facilitation of cancer progression [352, 353]. Polarization to M2 increases immunosuppression, and promotes gastric cancer cell migration [354] and peritoneal dissemination in gastric cancer [355]. Therefore, suppression of M2 with thiol methyltransferase 1A (TMT1A) inhibits lung adenocarcinoma progression [356]; and suppression by the tumor suppressor migration and invasion of migration and Invasion Inhibitory Protein (MIIP) via the STING-NFκB2-IL10 axis inhibits CRC progression [357].

Angiopoietin-related protein 1 (ANGPTL1) [358] which is highly expressed in endothelial cells in the adrenal gland, placenta, thyroid, heart, skeletal muscle, and small intestine, and is weakly expressed in the endothelium of the testis, ovary, colon, pancreas, kidney, and stomach, binds the ANGPTL1 receptor TEK tyrosine kinase (TIE2, cluster of

differentiation 202B, CD202B) on endothelial and early hematopoietic cells [359]. Inhibition of TIE2 decreases pathologic angiogenesis [360].

Activin A (ActA) secreted by breast cancer cells induces lung collagen deposition by lung fibroblasts in mice. Moreover, high ActA levels are associated with lung metastasis relapse and poor survival [361].

Platelets and tumor-associated platelets (TAPs)

Platelets in liver sinusoids bind the sinusoidal endothelium, interact with Kupffer cells, and traverse the space of Disse [362–364]. Subsequently, they increase hepatocyte growth factor (HGF) in hepatocytes and lead to cell proliferation [365, 366].

TAPs are found in prostate cancer [367] and peritoneal metastatic gastric cancer [368]. TAPs secrete matrix MMPs [369, 370], angiopoietin [371], vascular endothelial growth factor (VEGF) [372, 373], secretogranin III, cyclophilin A, calumenin [374], and CXCL12 [375].

TAPs cover cancer cells and allow them to migrate freely without being recognized by the immune system [376, 377]. TAPs recruit integrin alpha M (CD11b) positive (CD11b+) MMP-9+ granulocyte marker Ly6G positive (Ly6G+) granulocytes, which increase the number of lung metastases [378].

In patients with CRC, exosomes derived from platelets (PLT-Exos), in contrast to those from healthy individuals, contain LINC00183, which enhances the proliferative and invasive abilities of CRC cells [379]. LINC00183 participates in the β-catenin-LINC00183-miR-371b-5p-Smad2/LEF1 signaling pathway.

TAPs release exosomes (100 nm-1 μm) derived from α granules fused with the plasma membrane and surface membrane particles (30–100 nm) [380]. These microparticles contain integrin αIIbβ3, the GPIbα-IX-V receptor complex, P-selectin, CXCR4, bioactive lipids such as LPA and sphingosine-1-phosphate (S1P), cytoplasmic and secreted proteins, VEGF, angiopoietin-1, anti-vascular growth factors, such as endostatin, TGFβ, platelet factor 4, serotonin, proteases, VEGF, and C-X-C motif chemokines, including C-X-C motif chemokine 1 (CXCL1, GRO-α), PF4, C-X-C motif chemokine 5 (CXCL5), platelet basic protein (C-X-C motif chemokine 7, CXCL7), IL-8, and CXCL12 [381–386].

TAPs increase TGFβ and NF-κB signaling [387, 388], TGFβ-docking receptor GARP (glycoprotein A repetitions predominant), P-selectin [389, 390], αIIbβ3 [391], α6β1 [392], CXCL5 and CXCL7 [378], and serpin family E member 1 (SERPINE1) encoding plasminogen activator inhibitor 1 (PAI-1), thus enhancing the migration and invasion of tumor cells [393].

Inhibition of TAPs significantly decreases metastasis [394], which is concordant with using P-selectin targeting nanoparticles by simultaneously inhibiting chronic inflammation [395], and by aspirin, reducing TXA2 [396].

Cancer cells secrete and deposit the ECM proteins collagen and type I collagen through the chaperone heat shock protein 47 (Hsp47) [397]. Hsp47 increases platelet recruitment and cancer cell colonization in the lung. Therefore, platelets are important in cancer progression and metastasis [398]. Two isoforms of cyclooxygenase are necessary for arachidonate conversion to prostaglandin G2 (PGE2), and the subsequent production of prostaglandin H2 (PGH2), which promotes carcinogenesis and metastasis [74].

Platelets express the cyclooxygenase 1 (Cox-1) isoform, which is responsible for TXA2 synthesis, and induces platelet activation and aggregation [398]. Cancer cells express the cyclooxygenase 2 (Cox-2) isoform, thus generating PGE2. Aspirin acetylates serine residue 530 and thereby inactivates Cox-1 activity irreversibly, and consequently decreases TXA2 synthesis, platelet aggregation and metastasis.

Elastase and TAPs

Selectins are transmembrane glycoproteins that mediate heterotypic cell-cell contact through Ca2+-dependent interactions with cell-surface carbohydrates [399]. Ligands for E-selectin include sialyl Lewis X (sLe^x) and sialyl Lewis A (sLe^a, CA19–9) antigens [400, 401]. Activated platelets release endothelial cell activation factors, such as E-selectin with consequent cancer cell adhesion [399 *reviewed in* 402]. E-selectin has been reported to be elevated in adjacent hepatic metastatic CRC tissue and in serum [403, 404], although another study indicated no correlation [405].

Serum E-selectin levels are high in liver metastatic CRC but not in CRC without M1 [406, 407]. Simultaneous increases in E-selectin and sLe^a lead to higher levels in patients with CRC with lung and liver metastasis compared with patients without metastases [402].

Part 8: Immune evasion

The transmembrane glycoprotein CD154 (renamed from CD40 ligand, CD40L, pg39, TRAP) consists of a 215 aa extracellular moiety, a 24 aa membrane portion, and a 22 aa cytoplasmic domain, and has a mass of 39 kDa [408–412]. It was identified by monoclonal antibodies on B-cells [413, 414] and is expressed on epithelial cancers [413, 415–417]. The cDNA clone was isolated in 1989 [418]. Currently, CD154 is known to be expressed on CD4+ T lymphocytes, and platelet activation leads to conversion of CD154 to soluble sCD154 through shedding [419]. The activation of platelets is associated with measurable sCD154 in blood [420].

CD154 is highly expressed on platelets, mast cells, basophils, B-cells, and T-cells [415, 421–424], and activates platelets by binding the integrin glycoprotein αIIbβ3 (CD41/CD61, glycoprotein IIb/IIIa).

CD154 serves as a ligand for the CD40 receptor binding a soluble CD40, transcripted form the Cd154 gene on long arm of the X chromosome region, q26.3–q27.1, and belongs to the TNF family. TNF-α decrease the NAD(+)-dependent class III protein deacetylase SIRT1, followed by CD40 increase in the endothelium in a time- and concentration-dependent manner [425], together with miR21 [426].

CD154 induces GM-CSF release by endothelial smooth muscle cells with monocyte activation [427]. CD154 is also induced by T-cells via the T cell receptor (TCR) after antigen recognition, independently of CD40, or αIIbβ3 integrin or B-cell activation [428, 429]. Cancer cells increase IL-12-dependent CD154 expression and inhibit apoptosis [430]. CD154 induces an increase in thromboplastin (tissue factor, TF, CD142) [412]. TF is expressed in epithelia and on cancer cells, thus explaining its associations with cancers of the stomach [431], colorectum [432], liver [433], lung [434], breast [435], prostate [436], pancreas [437], and cervix [438].

Chemokine (C-C-motif) ligand 2 (CCL2; monocyte chemoattractant protein 1 (MCP1)) is secreted by macrophages [439] and recruits various immunocompetent cells [440, 441]. Consequently, granulocyte-macrophage colony-stimulating factor (GM-CSF) is secreted by activated macrophages, monocytes, mast cells, neutrophils, fibroblasts, endothelial cells and T-cells [442], thus resulting in monocyte differentiation by GM-CSF to anti-

tumorigenic macrophages [M1], and subsequent increases in interleukin 4 (IL-4), interleukin 6 (IL-6), tumor necrosis factor alpha (TNFα), CXCL10, and interleukin 27 (IL-27) secretion by macrophages [443]. The pro-tumorigenic macrophages [M2] are induced later in the process.

Platelets for blood transfusion have high levels of membrane-bound CD154 and soluble sCD154 both of which stimulate CD40+ cells [444]. CD40+ is expressed next to B cells, on monocytes, macrophages, microglia, dendritic cells, keratinocytes, endothelial cells, thymic epithelial cells, fibroblasts, and neurons [445–450].

Normal lung fibroblasts do not express CD40+ in contrast to bronchial fibroblasts [447]. CD40+ binding results in IL-6 increases and fibroblast proliferation [451]. NF-kappa B mobilization precedes CD40-mediated IL-6 production [452]. CD40+ increases Cox-2 and consequently the pro-inflammatory PGE-2 [453].

Chronic inflammatory cytokines such as IL-6 and IL-1 increase ICAM-I (CD54) but not CD40 [454]. CD154+ cells increase adhesion via E-selectin and intercellular adhesion via ICAM-1 and VCAM-1 [455]. In parallel, thrombin rapidly induces CD154 expression on platelets with co-expression of the receptor of CD154 and CD40, and is followed by inflammatory signaling on endothelial cells [456]. In this regulatory mechanism, after signaling and platelet aggregation, sCD154 is released.

Stimulation of CD40 increases cell motility [457], and high CD40 is associated with the aggressiveness of gastric cancer with lymph [458] and liver [459] metastases. Inhibition of CD40 with soluble CD40 ligand (sCD40L) decreases cell growth, induces apoptosis, and results in G0/1 phase arrest [460]. CD40+ gastric cancer cells upregulate CXCR5 with myeloid-derived suppressor cells (MDSC) migration and accumulation with immune escape [461].

Elevation of the activated platelet marker, CD154 ligand (CD40L), is associated with gastric cancer progression and metastasis [462]. Intriguingly, *H. pylori* in gastric cancer increase upregulation of cancer stem cell formation (CD55), downregulate immune regulation (CD40 and CD186) with immune escape, suppresses cell adhesion (CD44), neutrophil adhesion (CD54), and iron transfer (CD71), which are associated with increased aggressiveness [463].

SIRT1 deacetylates the RelA/p65 subunit of NF-κB [31] and regulates CD40 expression by downregulation in endothelial cells, thus enhancing neutrophil and peripheral blood mononuclear cell (PBMC) migration independently of IL-1β, IL-8, and monocyte chemoattractant protein-1 (MCP-1) [464].

Homodimeric receptor oligomerization of CD154/CD40 has been demonstrated [465] to be necessary for homeostasis [77]. CD154 activates the endothelium by upregulating adhesion molecules through IL-6 in a Cox-2-dependent manner [466].

Stimulation of epithelial cells with IL-6 increases fibrinogen [467]. Subsequently, fibrotic remodeling via IL-6 induces chronic inflammation followed by SRC family kinase (SFK)–Yes-associated protein (YAP) signaling dependent EMT [468]. LOX is then induced [469], and consequently induces IL-6 [470]. IL-6 induces downregulation of the tumor suppressor p53 [471].

YAP-dependent matrix remodeling signaling and crosstalk have also been reported. CAFs induce YAP/transcriptional coactivator with a PDZ-binding motif (TAZ), followed by actin-binding protein anillin (ANLN) and actin-elongation regulator Diaphanous-Related Formin 3 (DIAPH3) [472].

Omega-3 polyunsaturated fatty acids play important roles in carcinogenesis and metastasis [74]; suppress MMP-9 in CAFs both *in vitro* and *in vivo* [473]; and protect the peritoneal mesothelial-mesenchymal transition (MMT) through the FFAR4/CaMKKβ/AMPK/mTOR signaling inhibiting fibrosis and remodeling [474].

Major histocompatibility complex (MHC) discovery

The discovery of the MHC by Peter Alfred Gorer (1907–1961), Karl Landsteiner (1868–1943), Clarence Cook Little (1888–1971), George Davis Snell (1903–1996), Jean-Baptiste-Gabriel-Joachim Dausset (1916–2009), and Baruj Benacerraf Lasry (1920–2011). Gorer discovered the H-2 complex in 1936 [475, 476]. Little, the founder of the Jackson Laboratory (JAX), performed tumor transplantation with various strains and observed rejection of strains of host versus donor models [477]. Landsteiner, who discovered the blood groups in 1901, identified the Rhesus factor together with Alexander Solomon Wiener (1907–1976), who discovered the Polio virus in 1909 and demonstrated in 1945 that antibodies can be produced against any molecule and later presented to the immune

system [478]. Snell identified the H-2 locus in mice in 1951 [479]. Dausset discovered the first HLA antigen MAC (currently HLA-A2) in 1958 [480]. Benacerraf, in 1961, published observations indicating that random-bred animals immunized with antigens with restricted heterogeneity, such as hapten conjugates of poly L-lysine, are distributed into two groups, responders and nonresponders, and that the immune response regulates the interactions of the immune system [481]. Snell, Dausset, and Lasry were awarded the Nobel Prize in 1980 for their discovery of the major histocompatibility complex genes.

Part 9: Podoplanin (PDPN)

PDPN is a transmembrane glycoprotein receptor expressed in lymphatic vessels but not on the endothelium [482, 483]. PDPN was first found to be induced by carcinogenic chemicals (such as phorbol esters/TPA) in osteoblastic cells [484].

POSTN is strongly expressed by fibroblasts and it deposits in the peritoneal cavity in patients with encapsulating peritoneal sclerosis undergoing peritoneal dialysis [485]. This is also triggered by PDPN-positive mesenchymal cells [486]. PDPN-positive fibroblasts are associated with poor outcomes in epithelial cancers [487] and are known to differentiate POSTN-promoting metastasis through YAP and AKT in gastric cancer [488].

PDPN functions in the embryological development of the lymphatic vessels, kidneys, lungs, and brain [489]. PDPN is important in cell migration and it links actin cytoskeleton forming protrusions important for migration via CD44 [490]. It is associated with chronic inflammation [491], EMT [491], and ECM remodeling [492]. PDPN acts as a ligand for the C-type lectin-like receptor 2 (CLEC-2) receptor on platelets, thus triggering aggregation [493, 494]. CLEC-2 was identified in 1998 as the platelet receptor for the snake toxin rhodocytin in promoting aggregation [493]. Furthermore, PDPN is expressed on T_H17 cells [495, 496] and macrophages [497, 498].

PDPN has been identified in non-epithelial cancers, e.g., Kaposi's sarcoma [499], angiosarcoma [500], testicular germ cell tumors [501], and peritoneal mesotheliomas [502, 503]. PDPN has also been identified in epithelial cancers of the head and neck [504], esophagus (ESCC) [505, 506], stomach (particularly with relatively low differentiation and high aggressiveness) [507], colorectum [508], pancreas [509], liver [510], breast [511], ovary [512], cervix [513], in lung adenocarcinoma [514] and in squamous cell cancer [515].

However, PDPN has been first reported not to be expressed in HCC, intrahepatic cholangiocarcinoma, and metastatic liver cancer [516], and otherwise later reported to be expressed in HCC, particularly in peritumoral tissue plus at the vascular invasion front, and in CAFs [517]. Furthermore, PDPN is associated with various lymph node positive epithelial cancers [503]. Additionally, PDPN is expressed in the transition from the precursor of OSCC in oral leukoplakia (OL) to OSCC [518].

Mechanistically, M2 macrophages induce TGFβ with YAP/TAZ nuclear localization, and RhoA/ROCK/myosin induced cytoskeletal contractility, with ECM production and PDPN upregulation is seen with increased CRC cell proliferation [519].

PDPN is absent in the normal stroma, except for lymphatic vessels, but is expressed in CAFs, and is associated with metastasis and poor prognosis [520]. Inhibition of PDPN decreases cancer progression and metastasis in animal models of melanoma [521]; animal [522] and human squamous cell carcinoma [490]; osteosarcoma [523]; mesothelioma [524]; and human head and neck cancer [525].

High cancer cell expression of PDPN has been found to correlate with lymph node metastasis and diminished survival times in a cohort of 252 patients with OSCC [526]. Comparative transcriptional profiling of tumor xenografts has identified that this is mediated by endothelin-1, villin-1, and tenascin-C. Therefore, PDPN expression increases tumor lymphangiogenesis and metastasis to regional lymph nodes in vivo, without promoting primary tumor growth.

PDPN positive CAFs induce angiogenesis through AKT/NF-κB activation and the CCL2-ACKR1 axis in gastric cancer [527], and induce POSTN through YAP/AKT in gastric cancer-associated liver metastasis [528].

PDPN acts as a lymphocyte inhibitor [529] and induces the transformation of latent transforming growth factor beta-binding protein 1 (LTBP1) positive CAFs, which is followed by TGFβ signaling and CCL11 secretion. Subsequently, HSC activation is followed by recruitment of $CCR3^{+}$ metastatic gastric cancer cells to the liver [530].

Direct platelet–OSCC contact induces PDPN expression, and integrin β1 increases metastases [531].

Tetraspanin family member CD9 (Tspan 29) is an integrin-associated membrane protein with four membrane-spanning domains, and short and large extracellular loops [532]. CD9 inhibits the complex building of T1α (Aggrus)–PDPN induced platelet aggregation by complex building with transmembrane domains 1 and 2 (TM1 and TM2) of CD9, and thus suppresses pulmonary metastasis in vitro in HT1080 epithelial cancer [533].

Part 10: Cell transition plasticity

Cell transition plasticity is fundamental to not only embryology and development but also to carcinogenesis and metastasis, and it markedly increases the extensive heterogeneity in cancer and metastasis.

The heterogeneity of carcinoma cells expressing mesenchymal markers is known [534, 535]. EMT activation is associated with metastasis and the formation of cancer stem cells, but multiple intermediate, quasi-mesenchymal cell types with various phenotypes are generated during EMT [536]. Cells are kept in a quasi-mesenchymal cell state by ΔNp63 and p73, which together induce EGFR [537]. Decreases in ΔNp63 and p73 expression induce a change from the quasi-mesenchymal cell state of cancer stem cells to carcinoma cells without generating lung metastasis in breast cancer cells likely because these cells are in a highly mesenchymal state. Moreover, the induction of a more mesenchymal state makes cancer stem cells more aggressive. Identifying single EMT states is challenging because EMT programs generate multiple alternative cell states, and phenotypic plasticity permits frequent interconversions between these states.

Aggressive basal-like breast cancers show enrichment of cancer stem cells with low GATA3 and FOS inducing (high) FOSL1, thus promoting mesenchymal traits and decreasing epithelial features for which the AP-1 family protein FOSL1 is needed [538]. A comparable shift in glioblastoma to the more aggressive mesenchymal state is induced by FOSL1 [539, 540]. FOSL1 also forms complexes with the transcription factor AP-1, a Ras mediator [541].

High FOSL1 is known to be elevated and to promote metastatic aggressiveness in various epithelial carcinomas, such as those of the pancreas [542, 543], stomach [544], esophagus [545], head and neck [546, 547], breast [548–550], bladder [551], colorectum [550, 552–554], lung [550], and prostate and thyroid [550].

Cancer stem cells with high cell-surface expression of integrin β4 (ITGB4) also have elevated aggressiveness [535]. Furthermore, exosome transmitted FOSL1 from CAFs activates ITGB4 with chemoresistance and elevated aggressiveness [555]. FOSL1 from CAFs also drives cancer progression in HCC with polarization of pro-tumorigenic M2 macrophages [556].

In immortalized cells, FOSL1 induces EMT with detachment of cancer cells and budding, followed by MET with colonization [534, 557]. Moreover, FOSL1 is associated with chemosensitivity, but high FOSL1 expression has been suggested to explain delayed tumor relapse after chemotherapy, and its complete absence is prognostic for rapid relapse [558]. FOSL1 promotes loss of dormancy in cancer stem cells and thereby enhances chemosensitivity. Increased FOSL1 is associated with chemoresistance in dormancy, whereas its knockdown eliminates chemoresistance in breast cancer.

Part 11: CAFs and metastasis-associated fibroblasts (MAFs)

NSCLC induces interleukin 26 (IL-26) activated JAK-STAT3 signaling and CX3CL1 activated JAK-STAT3 and AKT-mTOR pathway, thus promoting CAFs involved in brain metastasis, followed by EMT, and progression [559]. CAFs facilitate TAM recruitment together with immune suppression, thus enhancing pro-tumorigenic macrophage polarization (M2) [560], which is associated with nuclear stress protein nuclear protein 1 (NUPR1) upregulation [561].

NUPR1 is involved in cancer proliferation and metastasis of various epithelial cancers, such as those of the breast, pancreas, or liver [562–565]. Moreover, it acts as a stress-induced transcription factor [564, 566]. NUPR1 is particularly overexpressed in early cancer stages but not in locally advanced stages [567]. NUPR1 expression depends on the nuclear translocation of YAP [568].

NUPR1 activation is induced through various routes, such as by lipopolysaccharide [569, 570], TGFb via Smad2/3 and Smad4 signaling [571, 572], or activation of transcription factor 4 (ATF4) [573]. NUPR1 induces autophagy associated with cancer proliferation and metastasis [574–576]. Furthermore, both *in vitro* and *in vivo*, NUPR1 directly binds the enzyme poly(ADP-ribose) polymerase (PARP) and inhibits its enzymatic activity [577].

PARP inhibition decreases BRCA1 at the protein level as well as RAD51 [578]; moreover, BRCA1 is essential for the repair of double-stranded DNA breaks (DSBs) [579]. Inhibition of BRCA1 tumor suppressor activity is mediated by binding of the transcription factor E2F to the tumor suppressor proteins p130 (retinoblastoma-like protein 2, RBL2)/p107 (retinoblastoma-like protein 1, RBL1). Notably, no BRCA1 mutation is needed. Inhibition of NUPR1 antagonizes pancreatic cancer cell growth [580] and induces cell death in HCC [581].

Moreover, 1,25-dihydroxyvitamin D3 inhibits NUPR1 in breast cancer [582]. NUPR1 mediates TGFβ-induced α-SMA expression, collagen synthesis by initiating Smad3 signaling, promoting EMT via fibroblasts in renal fibrosis [583]. Macrophages participate in regulating MAFs. JAK-STAT3 macrophage-fibroblast crosstalk is also associated with liver metastasis in pancreatic cancer [584]. The CAF interaction via CD74 and CD44 has been reviewed in detail: the cytokine macrophage migration inhibitory factor (MIF) phosphorylates CD74 activating CD44, followed by PI3K-AKT, NF-κB, and AMP-activated protein kinase (AMPK) signaling. This crosstalk occurs on the cell surface and is followed by immune evasion.

Another form of immune evasion occurs, for example, in EBV evasion of the T-cell response through CD74 downregulation [585].

Intranuclearly, transcription is regulated, e.g., by the bromodomain PHD finger transcription factor (BPTF) associated protein of 18 kDa (BAP18, MGC49942). BAP18 is encoded by the gene chromosome 17 open reading frame 49 (C17orf49). C17orf49 and HMG2L1 have been identified as subunits of the human nucleosome remodeling factor (NURF)/BPTF complex, and its H3K4me3 interaction with BPTF which is why this uncharacterized open reading frame C17orf49 was named as BPTF associated protein of 18 kDa (BAP18) [586]. BAP18 is widely expressed on various tissues as well as cancers.

The NURF [587]/BPTF (NuRF/BPTF complex) [588] shifts nucleosomes, thus altering DNA accessibility and allowing transcription factor access. BPTF acts as a "reader" of epigenetic marks, and its PHD domain binds H3K4me2/3, whereas the bromodomain binds acetylated histones (H4K12ac and K16ac) [589]. BPTF mutations lead to defects in thymocyte maturation and cell differentiation, particularly in the maturation of T cells

[590–592]. BAP18 is a direct DPY-30-interacting protein and knockdown of DPY-30 in fibroblasts leads to a senescent phenotype [593].

BAP18 acts primarily in the nucleus as a chromatin remodeler that boosts oncogenic pathways through Wnt signaling. In NSCLC, BAP18 interacts with the β-catenin, actin-like 6A (ACTL6A), and polymerase associated factor (PAF1) complex, and consequently increases protein expression of CCND1, c-myc, and CD44; cell proliferation; migration; and tumor growth [594, 595]. BAP18 is upregulated and acts as an oncoprotein, activating oncogene S100A9 promoting tumor progression, proliferation and metastasis in triple negative breast cancer [596], prostate cancer [597], liver cancer [598], and BAP18 modulates CCND1/2 transcription and promotes OSCC progression [599]. BAP18 expression markedly inhibits the proliferation of prostate cancer cells, whereas its depletion decreases the mRNA expression of a subset of AR target genes, including FASN, FKBP5, UBE2C, and PSA. Moreover, BAP18 facilitates the recruitment of MLL1 complex components that subsequently lead to enhanced H3K4me3 and H4K16ac levels at androgen-response elements of AR target genes [597].

Furthermore, BAP18 induces enolase 2 (ENO2), thus increasing cancer cell proliferation and angiogenesis, and shifting TAM polarization toward the M2 phenotype [600]. In contrast, BAP18 knockout or degradation by melanoma-associated antigens A3 and A6 (MAGE-A3/6) in a CRC cell line has been found to increase mobile cancer cells [*publication on preprint server pending submission; not peer-reviewed;* 601].

Single-cell RNA sequencing (SCRNA seq) withon a GEO dataset, clustering, annotation with trajectory, and cell-cell interaction analysis of breast cancer and secondary sites have indicated that two metastatic biomarkers, Neuropeptide Y (NPY) receptor Y1 (NPY1R) and Coiled-Coil Domain Containing 102B (CCDC102B), are expressed exclusively by MAFs [602]. CCDC102B, via activation of NF-κB, promotes metastasis [603]. The peptide NPY is expressed on various neuronal and non-neuronal tissues, and platelets serve as a reservoir for NPY [604, 605]. Information is consequently conveyed through Y1R-to-y6R receptor binding [606]. Beyond its roles in embryology, and neuromodulatory functions in the brain and peripheral nerves [607, 608], NPY influences various homeostatic processes, such as inflammation, the immune response, and bone metabolism [609].

Epithelial membrane protein 1 (EMP1) positive HSCs directly trigger the progression of hepatic fibrosis to HCC among others also through NPY1R [610]. Furthermore, direct crosstalk exists between sympathetic nerve-derived NPY, NPY1R, and TGFβ signaling in cancer cells expressing TβRI in OSCC [611]. NPY and NPY1R are upregulated, e.g., in pancreatic cancer, and inhibiting the NPY/NPY1R signaling axis decreases liver metastasis [612].

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