# Supplemental Material

# Epistemology of the Origin of Cancer II: Fibroblasts Are the First Cells to Undergo Neoplastic Transformation

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**Supplement Part 1**

**Cancer basics**

Cancers are routinely classified by their location [1]. Approximately 90% are therefore deemed to be epithelial cancers, followed by sarcomas (i.e., tumors of connective tissues, including bones, cartilage, muscle, fat, or tendons), leukemias (in the blood/bone marrow), lymphomas (in glands and lymph nodes), myelomas (also in the bone marrow and blood) and central nervous system tumors (in the brain or spinal cord). Histopathologically, cancers are also subdivided by cell type and morphology. For example, epithelial carcinomas are divided into adenocarcinomas and squamous cell carcinomas. The classification was necessary to create a system that would facilitate the analysis of cancers associated with various epidemiologies, countries, histologies, and responses to therapy, among other reasons.

Malignant tumors represent a group of heterogeneous diseases. Great efforts have been made to describe these tumors systematically. Several international agencies made important contributions to the diagnosis and treatment of cancer. Among these, the Union for International Cancer Control (UICC; previously named the International Union Against Cancer) was founded in 1933, followed in 1948 and 1959 by the World Health Organization (WHO) and the American Joint Committee on Cancer (AJCC), respectively. In 1950, the WHO developed a committee that focused on tumor nomenclature and statistics as an attempt to develop a systematic approach to classifying cancers [2]. In 1965 the UICC released an illustrated guide to tumor nomenclature [3]; this was followed in 1968 by the first edition of the TNM (tumor/nodes/metastases) classification of malignant tumors [4]. The WHO released another tumor classification system in 1976 [5] followed by the AJCC's first edition of the manual for staging cancers in 1977 [6].

Tumors can be distinguished macroscopically by either exophytic (outward) or endophytic (inward) growth. A malignant tumor can also be classified pathologically by a systemic overview and

identification of its putative tissue of origin (i.e., histogenesis). This resulted in the classification of these malignancies as epithelial tumors, mesenchymal tumors, special forms of mesenchymal tumors, special forms of mixed endothelial-mesenchymal tumors, neuroendocrine tumors, neuroectodermal tumors, germ cell tumors, and tumors of the embryogenic tissues (also known as dysontogenetic tumors).

Epithelial tumors are believed to be derived from the epithelium, including squamous epithelial cells (squamous cell carcinoma), basal cells (basalioma), transitional epithelial cells (urothelioma), or glands (adenocarcinoma). Mesenchymal tumors are thought to be derived from connective tissue and its derivatives, including mesenchymal structures formed together with gelatinous connective tissue, embryonic connective tissue, and the following tissues which are derived from the mesenchyme: loose, tight, and reticular connective tissue, bone and cartilage, smooth and cardiac muscle, kidney and the adrenal cortex, the hematopoietic system, and blood and lymph vessels. Therefore, mesenchymal tumors are classified based on their associations with connective tissue and its derivatives (fibrosarcoma, aggressive fibromatosis, myxosarcoma, and pleomorphic undifferentiated sarcoma), adipose tissue (liposarcoma), cartilage (chondrosarcoma), bone (osteosarcomas), synovium (synovial carcinoma), smooth muscle (leiomyosarcoma), skeletal (also known as striated) muscle (rhabdomyosarcoma), blood and lymphatic vessels (haemangiosarcoma, lymphangiosarcoma), peripheral nerves (malignant peripheral nerve sheaf tumor [MPSNT]), the mesothelium (malignant mesothelioma), the meninges (malignant meningioma), or granulosa cells (granulosa cell tumor).

Special forms of mesenchymal tumors include those associated with the bone marrow (acute myeloid leukemia, chronic myeloid leukemia, and Ewing's sarcoma), plasma cells (multiple myeloma), and the lymphatic system (both Hodgkin and non-Hodgkin lymphoma). Special forms of mixed endothelial-mesenchymal tumors include adenosarcomas, as well as adenosarcomas and

carcinosarcomas of the endometrium. These tumors are often called collision tumors as they consist of a mixture of epithelial and mesenchymal cells.

Neuroendocrine tumors are believed to originate from the neuroectoderm, and endocrine cells from various tissues and organs (e.g., carcinoid, malignant pheochromocytoma, adrenocortical carcinoma, and malignant insulinoma). Neuroectodermal tumors contain epithelial cells from the neuroectoderm, including astrocytoma, glioblastoma, anaplastic meningioma, and malignant melanoma. Germ cell tumors are associated with germ cells (e.g., malignant teratoma, seminoma) and ovarian cells (e.g., dysgerminoma). Tumors of the embryonic tissue are also known as dysontogenetic tumors (e.g., embryonal carcinoma, nephroblastoma, neuroblastoma, medulloblastoma, retinoblastoma, hepatoblastoma, and chorionepithelioma).

The following are characteristics of cancer cells that are frequently observed: little to no response to proliferation-regulating signals, genetic instability, and the ability to escape from replicative senescence, as well as the capacity to avoid terminal differentiation and apoptosis; cancer cells also exhibit both invasive and metastatic potential [7]. However, observations reflecting cancer cells in an advanced state and/or in which carcinogenesis has already occurred cannot be necessarily construed as causal in nature. As we discussed in an earlier publication, finding an apple in a car is not proof positive that apples grow in this location [8].

Nonetheless, most researchers assume that these cancers developed at the sites where they were first detected. Many observations to the contrary cannot be readily explained. For example, malignant cells lose contact inhibition compared to healthy cells, which may be why their mitotic activity is controlled by glycolipids with alpha-glycoside linkages. Likewise, certain epithelial tumors lose cell specificity. Likewise, the basal membrane protein laminin-5 can be produced by epithelial cells. This observation reveals their capacity for mesenchymal activity, with deposition mediated by the fibroblast meshwork found beneath the basal membrane [9].

Laminin 511, together with collagen IV, laminin 332, laminin 311, nicogen-1, and the perlecan component of the basal membrane actively inhibit immune cell migration by strengthening E-cadherin and decreasing expression of CD99L2 [10, 11]. CD99L2 in turn triggers oncosuppressor signaling.

Although it is possible to differentiate between epithelial and mesenchymal cells using immunohistochemical methods, the fact that these cells are profoundly heterogeneous [12] is not well-understood. Human lung fibroblasts undergo mesenchymal-epithelial-transition (MET) which leads to overexpression of epithelial markers and suppression of mesenchymal markers. This phenotypic change is associated with strong expression of E-cadherin in the absence of α-SMA [13]. Furthermore, bone morphogenic protein-7 (BMP7, also known as osteogenic protein-1 or OP-1) induces MET in adult renal fibroblasts [14]. EMT results in the loss of epithelial characteristics and the acquisition of mesenchymal traits [15]. In principle, it is not surprising that large variations in cells with epithelial and mesenchymal phenotypes are observed [16].

The aforementioned examples highlight the various cell shapes that represent human diversity; as suggested by these findings, each cell is unique and emerges at a different time, thereby explaining the extent of heterogeneity observed. One important issue revealed by this consideration is the possibility that what we observe under the microscope (e.g., a neoplastic epithelial cancer within the epithelium) may actually be derived from another cell type that has undergone transition. In this case, it will be critical to have some way of identifying and characterizing the cell that initially underwent normal-to-cancer-cell-transition (NCCCT). This question might be addressed via an in-depth study of the ultrastructure of the epithelium and its layers from normal tissues as well as from those with epithelial cancer. The concept of the precancerous niche (PCN) will also need to be considered.

**Supplement Part 2**

**Recent evidence (since 2019)**

Our original publication entitled "*Epistemology of the Origin of Cancer*" [17] introduced a six-step process that led to carcinogenesis that included signaling, contributions of both anti- and pro-inflammatory mediators, mechanotransduction, the precancerous niche (PCN), and events associated with cell transition. Taken together, these steps facilitated a deeper understanding of the development of cancer [8, 17–31]. Since 2019, many reports with findings that support this paradigm have been published. These are discussed in the paragraphs to follow.

***Microbial pathogens and carcinogenesis***

Pathogenic stimuli are critical drivers of carcinogenesis. For example, Inaida and Matsuno [32] reported that a history of previous infections correlates positively with tumor incidence. Interestingly, single breast tumor samples are host to an average of 16.4 distinct bacterial species compared to <9 in all other tumor types; a total of 9,190 different bacterial species were detected in different tumors and normal tissues. By contrast, Nejman *et al.* [33] found that lung and ovarian tumors have bacterial loads that are similar to those of tumor-adjacent normal tissues. The role of microorganisms and their contributions to the origin of prostate cancer have received substantially more attention. For example, results of a published multivariate analysis revealed that the presence of *Propionibacterium acnes* (*P. acnes*) was associated with a four-fold increase in odds of developing prostate cancer after adjustment for age, calendar year of surgery, and smoking status (odds ratio [OR]: 4.46; 95% confidence interval [CI]: 1.93–11.26) [34]. Of note, human papillomavirus (HPV) is widely recognized as a cause of cervical and oropharyngeal cancers. Anti-HPV vaccines are available, and the increasing use of these prophylactic agents has been associated with as much as a 90% in the incidence of these cancers [35, 36].

Similarly, Epstein-Barr virus (EBV) has been implicated in 8–9% of gastric cancer patients [37]. A recent study reported that this number may be as high as 23%. In particular, EBV nuclear antigen 3 (EBNA-3) could be detected in 33% more individuals within a young-onset cohort (≤45 years), with no differences observed in the rate of EBV positivity between an Israeli and a German young-onset cohort [38]. A close relationship between NF-κB dysregulation and EBV- and Kaposi sarcoma herpesvirus (KSHV)-related cancers was reported [39].

Collectively, these findings suggest that an antimicrobial therapeutic approach might be valuable as a means to combat specific cancers. This approach has been evaluated for the treatment of cholangiocellular carcinoma (CCC). Gramicidin, which is a pentadecapeptide antibiotic from *Bacillus brevis* that inhibits early growth response 4 (EGR4) and subsequent CCC cell growth *in vitro* and *in vivo*. However, although EGR4 expression increased 14.5-fold in 80% of CCC patients, no correlation with survival was observed [40]. Currently, the anticancer potential of this specific approach remains unclear.

The carcinogenic impact of silent *Toxoplasma gondii* infection might also be underestimated. Two prospective studies highlighted the association of this infection with the risk of developing adult glioma [41].

Experiments performed in 1975 revealed that parasitic cells underwent mitotic arrest in response to the administration of the antihelminthic agent, benzimidazole (methyl 5-benzoyl-1H-benzimidazol-2-yl-carbamate) [42]. This compound has since been used as a treatment for echinococcosis [43]. Mebendazole alters the extracellular matrix via its impact on microtubule functions which is also associated with its anti-cancer activities [44, 45]. This drug has been evaluated as a treatment for adrenocortical cancer [46], melanoma [47], breast cancer [48], colorectal cancer [49], glioma [50, 51], ovarian cancer [52], thyroid cancer [53], and pancreatic cancer [54].

*Chronic inflammation, fibrosis, and mechanotransduction*

Greater attention might be paid to the consequences of asymptomatic, subclinical chronic inflammation and the activation of various signaling pathways and their contributions to carcinogenesis. The cytokine, transforming growth factor beta 1 (TGFβ-1) plays an important role in carcinogenesis, as activation of its signaling pathway can lead to an imbalance of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) [**17, 18, 23**]. Increased lysyl oxidase (LOX) activity induces extracellular matrix (ECM) crosslinking in primary human dermal fibroblasts via the actions of lysyl hydroxylase (LH) and the transglutaminase family enzymes [**56**]. LOX and its isoenzymes have a significant impact on the progression of cancer and have been associated with poor overall survival [**56–58**]. Interestingly, LOX and lysyl oxidase-like 2 (LOXL2) inhibitors were found to reduce cancer growth in a genetically-engineered mouse model of spontaneous breast cancer [**59**].

Similarly, 5-methoxy tryptophan (5-MTP), which is a component of the forkhead box protein O3a (FOXO3a) signaling cascade [**17, 18, 23**], inhibits TGF-β1-induced production of collagen I, collagen III, fibronectin, and alpha-actin-2 (αSMA). This results in increased FOXO3a activity and leads to decreased levels of micro RNA-21 (miR21) and attenuated fibrosis [**60**]. In this setting, 5-MTP is synthesized from L-tryptophan via the actions of tryptophan hydroxylase-1 (TPH-1) and hydroxyindole O-methyltransferase (HIOMT) and the suppression of cyclooxygenase 2 (Cox-2) [**61**]. Of note, 5-MTP is produced by vascular endothelial cells [**62**]; this may be of great importance given that vascular cancer is extremely rare. Furthermore, 5-MTP inhibits cell transition as well as cancer cell migration and metastasis [**63**] by downregulating TGF-β/smad family member 3 (Smad3) and phosphatidylinositide 3-kinase (PI3K)/protein kinase B (Akt) signaling [**64**]. These mechanisms reveal why findings that indicate increases in FOXO3a secondary to 5-MTP are concordant with the insights provided earlier and indicate that FOXO3a levels decrease as expected

[17, 18, 23] and are downregulated in breast cancer tissues; by contrast, overexpression suppresses cell transition and metastasis via its impact on the twist-related protein 1 (TWIST)/miR-10b/cell adhesion molecule 2 (CADM2) signaling pathway axis [65]. Importantly, FOXO3 also suppresses DNA double-strand breaks and thus associated mutations, genome instability, and genome rearrangements [66].

The interconnection with Yes-associated protein (YAP) in the multi-step carcinogenesis process [30] has also received increased attention. Hu *et al.* [67] reported that LOXL1 modulated the malignant progression of colorectal cancer (CRC) by inhibiting the transcriptional activity of YAP; this [67] is consistent with earlier findings indicating that decreased LOX1 levels will result in arrested fibrosis because elastin crosslinking has been reduced [68]. Fibrosis promotes cell transition via the actions of TGFβ, Snail, the zinc finger E-box-binding homeobox (ZEB), TWIST, RAS, mitogen-activated protein kinase (ERK, synonymous with MAPK), Smad, and Ras-responsive element binding protein 1 (RREB1) [69]. Moreover, miRNA-101 suppresses signaling via TβR-I and thus cell transition and renal fibrosis induced by TGF-β1/Smad3 signaling in a mercuric chloride ($HgCl_2$)- induced renal interstitial fibrosis (RIF) model [70].

Another example of the complexities involved in this process focuses on the actions of focal adhesion kinase (FAK; also known as PTK2, FADK, FAK, FAK1, FRNK, PPP1R71, p125FAK, pp125FAK, protein tyrosine kinase 2), as discussed in previous publications [18, 22, 26, 30]. FAK signaling has a substantial impact on cell migration and tissue repair [71]. FAK is required for wound healing, particularly in its dephosphorylated form. FAK is dephosphorylated by the enzyme, low-molecular-weight protein tyrosine phosphatase (LMW-PTP), which also inhibits integrin signaling. FAK inhibition suppressed cancer cell invasion and migration in experiments targeting ovarian cancer [18, 72, 73]. FAX also undergoes autophosphorylation at Tyr397. Interestingly, higher levels of phosphorylated FAK were detected in pancreatic cancer [74]. Similarly, higher rates

of pTyr397-FAK were also detected in gastric cancer [75]. Downregulation of pTyr397-FAK resulted in decreased levels of p-Akt and p-ERK together with the upregulation of E-cadherin and β-catenin [76]. Furthermore, pFAK also activates extracellular signal-related kinase 5 (ERK5) [76]. Fibronectin is another protein that merits further evaluation. Fibronectin increases FAK signaling via pPI3K and pAKT which leads to cell migration and invasion that can be inhibited by FAK siRNA [77].

FAK and paxillin both promote migration and adhesion to fibronectin [78]. Paxillin connects integrins to FAK; levels of this protein are increased in various states including cell hyperplasia, dysplasia, metaplasia, and cancer [79, 80]. Cellular signal transduction requires FAK together with adaptor protein p130Cas (Cas) and lamellipodin. Lamellipodin has a direct influence on cell cycle regulation [22, 81] and Rac-dependent guanosine triphosphatase is involved in FAK and ECM-mediated stiffening.

LOX activates FAK/Src signaling as well as the actions of Snail [82–84], whereas FAK/Src signaling promotes cell transition [85]. The isoenzyme LOXL2 attenuates glycogen synthase kinase (GSK)-3b-induced phosphorylation of Snail [86, 87].

Taken together, these findings explain how LOXL2 induces cell transition via FAK/Src signaling [83] in gastric [88], breast [89], and pancreatic cancers [82, 90]. Vinculin, which is a component of focal adhesion contacts, is a key regulator of cell migration. LOX knockdown decreases pTyr397-FAK and increases vinculin levels [91], based on its mechanistic connections that lead to the disruption of homeostasis in wound healing.

Oncostatin-M (OSM) is released in response to chronic macrophage activation together with TNF-α and interleukin beta 1 (IL-b1) which are cytokines that activate fibroblasts [92–94] as reviewed in [23]. Furthermore, the pleiotropic cytokine, interleukin (IL)-6, and OSM induce the expression of

the aryl hydrocarbon receptor (AHR) as well as NF-κB binding characteristic of HCC [95, 96] as reviewed in [29]. More recent evidence suggests that OSM promotes extracellular remodeling associated with LOXL2 upregulation in breast cancer [97] and explains why the 2019 Epistemology illustration might be enhanced. Results from previous work revealed that OSM co-regulated cell transition [98–101] and inhibited OSM during cell transition [103].

Several of these features, including chronic inflammation as well as fibrosis and its associated mechanotransduction have been effectively treated. For example, the application of mebendazole resulted in reductions in chronic inflammation as well as significant reductions in trichrome-positive fibrotic connective tissue and α-SMA-positive activated pancreatic stellate cells that are typically associated with fibrogenesis and reduced dysplasia and intraepithelial neoplasia compared to controls in a model of early-stage pancreatic cancer [54].

*Eicosanoid metabolism*

Previous studies have provided detailed information on the pro-inflammatory regulatory mediators derived from N-6 polyunsaturated fatty acid (ω-6-PUFAs) through dihomo-gamma-linolenic acid, (8Z,11Z,14Z)-8,11,14-Icosatrienoic acid (DGLA), arachidonic acid (AA), docosatetranoic acid (DTA) and osbond acid (BDPA) and lipoxygenase (ALOX), cyclooxygenase (Cox) and cytochrome p 450 (CYP) and result via 12-lipoxygenase (12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type, ALOX12), 5-lipoxygenase, 5-LOX (arachidonate 5-lipoxygenase, ALOX5), cyclooxygenases (Cox1, Cox2, and Cox3) and cytochrome P450 isoforms (CYP*) to 5E,8Z,10Z,14Z)-12-hydroxyicosa-5,8,10,14-tetraenoic acid (12-HETE), 6E,8Z,11Z,14Z)-5-oxoicosa-6,8,11,14-tetraenoic acid (5-oxo-ETE), leukotriene E4 (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-2-carboxyethyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid, LTE4), leukotriene B4, (5S,6Z,8E,10E,12R,14Z)-5,12-dihydroxyicosa-6,8,10,14-tetraenoic acid, LTB4) [ALOX12 and

ALOX5 metabolism with consequent 12-hydroperoxyicosa-5,8,10,14-tetraenoic acid (12-HpETE) and 6E,8Z,11Z,14Z)-5-hydroperoxyicosa-6,8,11,14-tetraenoic acid (5-HpETE)], 6-keto-prostaglandin F1alpha (7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]-6-oxoheptanoic acid, 6-keto-PGFα), prostaglandin D2, (Z)-7-[(1R,2R,5S)-5-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid (PGD2), 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), malondialdehyde, propanedial (MDA), prostaglandin D2 ((Z)-7-[(1R,2R,5S)-5-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid, PGD2) (Cox metabolism) and 20-hydroxyeicosatetraenoic acid (5Z,8Z,11Z,14Z)-20-hydroxyicosa-5,8,11,14-tetraenoic acid (20-HETE) and 20-hydroxy prostaglandin E2 (20-OH PGE2) and 20-hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,14Z)-20-hydroxyicosa-5,8,11,14-tetraenoic acid (20-HETE, CYP* metabolism) [24]. Results of recent studies also revealed that 20-HETE and epoxyeicosatrienoic acids (EETs) can promote cell proliferation and decrease apoptosis [103]. This provides additional evidence for the proposed cancer paradigm, together with the information in the following paragraph.

Anti-inflammatory regulatory mediators can be derived from N-3 polyunsaturated fatty acid (ω-3-PUFAs) via eicosatetraenoic acid (all-cis-8,11,14,17-eicosatetraenoic acid, ETA), eicosapentaenoic acid ((5Z,8Z,11Z,14Z,17Z)-eicosa- 5,8,11,14,17-pentenoic acid, EPA), docosapentaenoic acid (7,10,13,16,19-docosapentaenoic acid, DPA) and docosahexaenoic acid ((4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid, DHA) [24]. This results in the production of specialized pro-resolving lipid mediators (SPMs) such as resolvins (RVs), and maresins (MaRs) via the actions of various metabolic enzymes, including:

- aspirin-triggered cyclooxygenase 2 (AT-Cox2) or CYP* via 18-hydroxyeicosapentaenoic acid (18-hydroxyicosa-2,4,6,8,10-pentaenoic acid, 18-HpEPE) into resolvin E1

((5S,6Z,8E,10E,12R,14Z,16E,18R)-5,12,18-trihydroxyicosa-6,8,10,14,16-pentaenoic acid, RvE1), resolvin E2 ((5S,6E,8Z,11Z,14Z,16E,18R)-5,18-dihydroxyicosa-6,8,11,14,16-pentaenoic acid, RvE2), and resolvin E3 ((5Z,8Z,11Z,13E,15E,18S)-17,18-dihydroxyicosa-5,8,11,13,15-pentaenoic acid, RvE3);

- 15-lipoxygenase (15-LOX, 15-LOX-1, arachidonate 15-lipoxygenase, ALOX15) and 15-lipoxygenase type II (15-LOX-2, arachidonate 15-lipoxygenase type B, ALOX15B) through 17S-hydroperoxy-4Z,7Z,10Z,13Z,15E,19Z-docosahexaenoic acid, 17-HpDHA) into resolvin D1 ((4Z,7S,8R,9E,11E,13Z,15E,17S,19Z)-7,8,17-trihydroxydocosa-4,9,11,13,15,19-hexaenoic acid, RvD1), resolvin D2 ((4Z,7S,8E,10Z,12E,14E,16R,17S,19Z)-7,16,17-trihydroxydocosa-4,8,10,12,14,19-hexaenoic acid, RvD2), resolvin D3 ((4S,5E,7E,9E,13Z,15E,17R,19Z)-4,11,17-trihydroxydocosa-5,7,9,13,15,19-hexaenoic acid, RvD3), resolvin D4 ((4S,6E,8E,10E,13E,15Z,17S,19Z)-4,5,17-trihydroxydocosa-6,8,10,13,15,19-hexaenoic acid, RvD4), resolvin D5 ((5Z,7S,8E,10Z,13Z,15E,17S,19Z)-7,17-dihydroxydocosa-5,8,10,13,15,19-hexaenoic acid, RvD5), resolvin D6, (4S,5E,7Z,10Z,13Z,15E,17S,19Z)-4,17-dihydroxydocosa-5,7,10,13,15,19-hexaenoic acid, RvD6), and neuroprotectin D1 (NPD1);
- ALOX15 to maresin 1 ((4Z,7R,8E,10E,12Z,14S,16Z,19Z)-7,14-dihydroxydocosa-4,8,10,12,16,19-hexaenoic acid, MaR1), and
- through ALOX15 and ALOX15B through 15-hydroperoxy-eicosatetraenoic acid ((5Z,8Z,11Z,13E)-15-hydroperoxyicosa-5,8,11,13-tetraenoic acid, 15-HpETE) into lipoxin A4 ((5S,6R,7E,9E,11Z,13E,15S)-5,6,15-trihydroxyicosa-7,9,11,13-tetraenoic acid, LXA4), lipoxin B4 ((5S,6E,8Z,10E,12E,14R,15S)-5,14,15-trihydroxyicosa-6,8,10,12-tetraenoic acid, LXB4), and (5R,6R,7E,9E,11Z,13E,15R)-5,6,15-trihydroxyicosa-7,9,11,13-tetraenoic acid, (15-epi-LXA4) .

The recent literature features numerous studies that consider the role of anti- and pro-inflammatory mediators and their contributions to this cancer paradigm [104–112].

*Chronic stress escape strategy, the precancerous niche, and cell transition*

Physiologic protection strategies are effective with respect to the chronic stress escape strategy (CSES) until they become overwhelmed, for example, as cancer cells are capable of generating their own inflammatory responses that protect against virus infection [113]. This may be a critical step toward the creation of the PCN during carcinogenesis; it also may explain how the PCN contributes to the poor response to immunotherapy observed in pancreatic cancer, which appears to be undermined by FAK inhibition mediated by VS-4718 [26]. This response markedly reduces fibrosis and the recruitment of tumor-infiltrating immunosuppressive cells and eventually limits cancer progression; a two-fold increase in survival time was reported in a relevant mouse model [26, 30, 74].

It is also important to understand PCN responses to external radiation. The results of earlier studies revealed that radiation activates IKKβ/NFκB which enhances the transcription and synthesis of LOX. In these experiments, siRNA knockdown of IKKβ largely abolished LOX production. Triptolide (TPL) is a diterpenoid with three epoxide groups that inhibits pro-inflammatory signaling via TNF-α, MAP kinases, and IL-2. In animal models (e.g., mice and dogs), TPL prevented the nuclear translocation and DNA binding by NFκB which resulted in inhibition of the IKKβ/NFκB pathway and decreased LOX synthesis. The net result was an anti-cancer/anti-leukemia effect based on TPL-mediated alleviation of radiation-induced pulmonary fibrosis [114].

Synthetic TGF-β1 and Smad oligodeoxynucleotides inhibit cell transition and differentiation in kidney fibrosis *in vivo* and *in vitro* [115]. These findings are consistent with the results of experiments that explored the impact of synthetic antifibrotic Smad/Sp1 chimeric decoy

oligodeoxynucleotides [116]. Collectively, these findings provide further evidence to support the cancer paradigm presented here and highlight the fact that an antifibrotic approach may normalize the tumor microenvironment [117].

**Supplement Part 3**

**Fibroblasts: historical consideration**

In 1838, Johannes Müller (1801−1858), the teacher of Carl Bogislaus Reichert (1811−1883) and Rudolf Virchow (1821−1902), coined the term "malignant" to describe neoplasms that result in death secondary to tissue destruction and/or metastasis [118]. The first association between cancer and connective tissue may be attributed to Reichert in 1845 [119]. Our current cancer classification system is largely based on his work. The identification of epithelial cells as the origins of cancer facilitated the systematic classification of tumors of various organs and structures. This notion and classification system are still widely accepted. In earlier times, cancers were frequently referred to as epitheliomas. Also in 1845, Hermann Lebert (1813−1878) described cancer cells with large or prominent nuclei; while this finding was initially reported as non-specific, he also identified an alveolar framework (connective tissue) filled with cells as a criterion for malignancy [120]; this led to the use of the term "fibroblastic neoplasms" in France.

In 1858, Virchow stated "*...the vast majority of neoplasms arise from connective tissue or equivalent parts of connective tissue, and that the initial rudiments for all tumors are almost the same*" (in German, "…die grosse Mehrzahl der Neubildungen aus Bindegewebe oder dem Bindegewebe äquivalenten Theilen hervorgeht und dass die ersten Anlagen für alle Neubilundgen nahezu gleichartig sind…" [121]. Thus, Virchow was clearly of the opinion that connective tissue was at the origin of heteroplastic neoplasias and that different types developed based on the differentiation of the cells found in a given tissue. This was contrary to the belief that all carcinomas

were derived from cells of epithelial origin [122]. Similarly, Wilson Fox (1831–1887) also identified connective tissue as the basis for cancer development [123]. Virchow later qualified his initial hypothesis and stated, that "…*the formation of cancer starts with the development of epithelium at an improper site and, therefore, proof of the impropriety of the site (heterotopia) is the first step to diagnosis*" [124].

Fibroblasts were first described as a distinct cell type in 1858 by Virchow, who called them "*Spindelzelle des Bindegewebes*", i.e., spindle-shaped cells of the connective tissue [121]. In this regard, Professor John Goodsir provided Virchow with slides from a miner's lung that featured spindle-shaped cells [125]. These cells were also described in 1876 by Gowers in his study of sarcomas [126]. In 1881, the term "fibroblast" was first proposed by Ernst Ziegler (1849–1905) (in German, "*Die Bildungszellen des Bindegewebes bezeichnet man als Fibroblasten*") to describe cells that produce new connective tissue as part of the healing process [127] (p. 128)]. Fibroblasts were originally named epitheloid cells that were extremely variable in form. During the earliest stages of development, these cells were described as rounded; later they took on many different shapes, including club-, spindle- and star-shaped. Ziegler's observation was replicated by Santiago Ramón y Cajal (1852–1934) who observed "célula fusiforme" or "fibro-células" as essential producers of granulation tissue in healing skin wounds and scars [128, 129]. In 1897, Leo Loeb (1869–1959) reported that surface epithelial cells can move into the lower layers and transform into connective tissue; at the time, Loeb thought that connective tissue contained inactive epithelial cells [130]. However, during this time (as well as today), the general consensus was that epithelial cells could develop only from other cells of this origin (In German, "*Epithel entsteht nur aus Epithel...*") [131] (p. 121)].

We contend that Virchow's belief, in accordance with his famous principle "*omnis cellula a cellula*" (all cells are all direct descendants of other cells), and that the cell is the smallest living unit of the

human organism. Thus, our understanding of the basis of all pathological tissue changes was and remains correct.

Alexander Alexandrowitsch Maximow (1874–1928) provided these connective tissue cells with the name "ordinary fibroblasts" (in German, "*gewöhnlichen Bindegewebszellen*") [**132**] (p. 19). He described these cells as fairly large and flat with a round or mostly oval nucleus (in German, "*…ziemlich grossen, platten, runden oder meistens ovalen Kern*"). Intriguingly he reported that polyblasts can develop from fibroblasts that produce collagen intermediates. This gives rise to cell-forms which, when considered in a developed state, frequently appear to bear little resemblance to one another.

Fibroblasts have been recognized for many years as necessary for wound healing and creating connective tissue [**133**]. In 1890, these cells were described in cancer tissues by the Scottish pathologist William Russel (1852–1940) who described them as oval hyaline bodies in preparations stained with eosin and logwood or carbol fuchsin and iodine green; interestingly, these cells were not detected in fibromas, papillomas, myomata, or condylomata [**134**]. Russel reported that these cells could be found primarily at the margins of early cancers as well as within the stroma and lymphatics, albeit with many variations in size. Later on, these fibroblasts were named *Russel bodies*; Russel himself believed that these may have been an organism associated with cancer, possibly a fungus.

In 1869, Edwin Klebs (1834–1913) [*reviewed in* **133**], who had been Rudolf Virchow's (1821–1902) assistant, introduced paraffin embedding techniques to pathology as a means to achieve serial thin tissue sections of a standard thickness [**135**]. Klebs believed that fibroblasts were degenerative products associated with cancer [*reviewed in* **134**] this was echoed by other scientists [**136, 137**]. Sometime later, others described these cells as hematocytoblasts that contained Russell bodies [**138, 139** *reviewed in* **140**] or red blood corpuscles phagocytized by plasma cells [**141** *reviewed in* **140**]. At

some time even later, fibroblasts were described as intracellular bodies that resulted from the interactions between bacteria and primarily immunoglobulins [142]; however, a subsequent study using both light and electron microscopy study revealed no immunoglobulins and also explained why the earlier observations yielded such heterogeneous interpretations [143].

However, these bodies/cells were observed in numerous precancerous lesions, for example, in Barrett's esophagus [144], *Helicobacter pylori*-induced gastritis [145], rectal adenoma [146], pancreatitis [147], tubulovillous adenoma of the colon [148], human papillomavirus-18-induced cervicitis [149], and herpes simplex virus esophagitis [150]. We do not know if the aforementioned oval structures were the same in all material that was examined. While the different results that were reported may be related to the various fixatives and staining procedures that were performed, the critical interpretations of these findings may not be recognized. To the best of our knowledge, the role of fibroblasts as primary cells in neoplastic transformation has not been considered until now. These earlier studies focused on fibroblast structure and function in cancer tissues may need to be re-reviewed so that the various "bodies" and "cells" identified during this time in history might be evaluated more thoroughly.

As noted above, William Russell (1852–1940) was the first to describe oval hyaline bodies in these tissues [134]. However, oval cells had been described earlier, in 1911, as young connective tissue cells that were associated with decreases in "*collagenous fibers in number and very fine*" in the absence of inflammatory cells [133]. Similarly, in 1910, Carey described nuclei surrounding an oval or elliptical lumen enclosed in undifferentiated mesenchymal cells in the esophagus of a 9.5mm embryo [151]; when fixed, these cells formed a reticular coagulum. At a later point, mesenchymal cells were detected with various degrees of elongation. During this phase, myoblasts underwent rapid differentiation with nuclei that began as spherical and became oval but only maintained this latter shape for relatively brief intervals. This finding may explain the different observations and

may also indicate that an essential step in the development of cancer was not recognized. At the same time, the extracellular matrix and its influence on cell development were vastly underestimated, although our forefathers provided significant insights into its structure and function. Of critical note, during embryonic development, these oval-shaped cells are observed only rarely and during a very short period during cell differentiation.

Other issues also need to be taken into account. For example, based on results published in 1937 [152] and 1940 [153], Farber described "*small oval cells about the ducts and vessels in the portal areas of the anatomic liver lobule*" [154]. These oval cells had previously been described as components of granulation tissue [155–157] and were later reproduced in more detail [158].

The origins of hepatic oval cells are still discussed. While they can be detected after liver damage [159] in contrast to earlier assumptions [160] they are currently not thought to be from bone marrow [161]. Hepatic oval cells may be hepatic progenitor cells because they can differentiate into hepatocytes [162, 163]. Grisham [164] performed electron microscopic studies of tissues undergoing experimental hepatic degeneration and confirmed the existence of oval cells. The periportal regions of the liver contained connective tissue, vascular vessels (i.e., lymphatic, blood, and very small bile duct vessels), and nerve cells.

In an animal model of liver cancer in which rats were fed 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB) or 4'-fluoro-4-imethylaminoazobenzene (4'-F-DAB), the liver epithelium exhibited neoplastic changes, including adenomas once treatment were discontinued. Withdrawal of these treatments prevented further change in these areas but did not lead to regression. However, malignant transformation took place upon the resumption of dye feeding [157]. Most notably in response to feeding with 3'-Me-DAB, new bile duct cells were detected in areas of cholangiofibrosis; bile duct cells were transformed into parenchymal cells and malignant cancer arose from these areas of fibrosis. Price also described the responses of rats fed 3′-methyl-4-

dimethylaminoazobenzene as follows: "*The majority of the duct cells were replaced by parenchymal tissue and scattered islets of hyperplastic ducts persisted*". This is most likely why scientists classified this stage as hyperplasia or cholangiofibrosis. Tissues with more clearcut neoplastic findings were called adenomas.

In this regard, "…*preneoplastic lesions showed strong cytoplasmic staining of proliferating oval cells and of the cell outlines of hepatocytes, in areas of nodular hyperplasia*" [**165**]. The text went on to note as follows: "*Characteristically, small oval cells proliferate around bile ducts and blood vessels in the portal triad and infiltrate between sinusoids and hepatocytes in adjacent liver lobules…increased expression of actin-like contractile protein in preneoplastic as well as in neoplastic lesions*". Hepatic oval cells develop during a very early phase of carcinogenesis in 3'-Me-DAB-treated rats (i.e., three weeks after treatment of preneoplastic lesions) and, in contrast to hepatocytes, these cells express α-smooth muscle actin at levels comparable to stromal cells [**165**] and were otherwise similar to myofibroblasts [**166**]. In contrast to myofibroblasts, fibroblasts do not express α-SMA that incorporated α-SMA; this antigen is detected only in fibroblasts that have differentiated into myofibroblasts.

Furthermore, the differentiation of fibroblasts into myofibroblasts occurs in response to direct contact with neurites [**167**]. Physiological endoplasmic reticulum (ER) stress also mediates fibroblast differentiation [**168**]. As reported by Bischoff *et al.*, [**169**] contact-dependent asymmetry associated with cell-matrix adhesion drives their directional movement, while contractile actin filaments contribute to the integrity of the migrating cell cluster.

Oval cells can be detected only rarely in normal liver. Cytokeratin 7 (CK7) and cytokeratin 19 (CK19) are expressed in both oval cells and mature cholangiocytes at levels that are proportional to the degree of liver fibrosis in infants with cholestasis [**170**].

Variabilities in fibroblast differentiation can be understood in an analysis of fetal wound healing. Upon recognition of the possibility of fetal surgery [171] specifically, successful intrauterine surgery that does not interrupt the pregnancy or harm the fetus [172], wound healing in the fetus became a prominent focus. Interestingly, fetal tissues heal without scarring, collagen deposition, or induction of an inflammatory response [173, 174]. Even wounds that are sutured eventually heal without scars [175]. Fetal scarless wound healing occurs in the absence of myofibroblasts and the presence of lower TGF-β1 levels [176). Fetal serum and amniotic fluid are not critical components of this response, however, researchers have reported a switch to adult healing (and associated scar formation) during gestation once the fetal cells have differentiated [177, 178]. During normal wound healing, fibroblasts migrate actively secondary to actinomyosin contractility which also facilitates their adhesion. At a point during this process, α-SMA is incorporated into fibroblasts as part of the process of differentiation into myofibroblasts. By contrast, fetal fibroblasts exhibit a different contractile phenotype; healing that results in a scar is dependent on cell differentiation and function rather than the fetal environment; T-cell mediated inflammation is not necessary for this process [176].

**Supplemental Part 1-to-3 References**


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