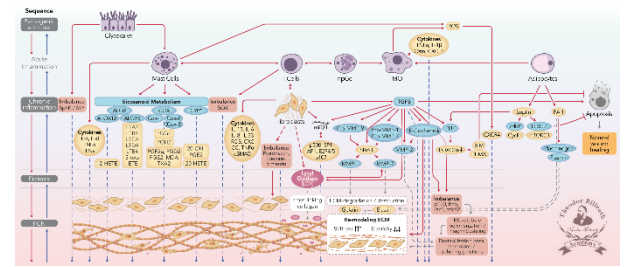


GRAPHICAL ABSTRACT – HIGHLIGHTS

1. Epistemology of the Origin of Cancer I (2014, 2019)

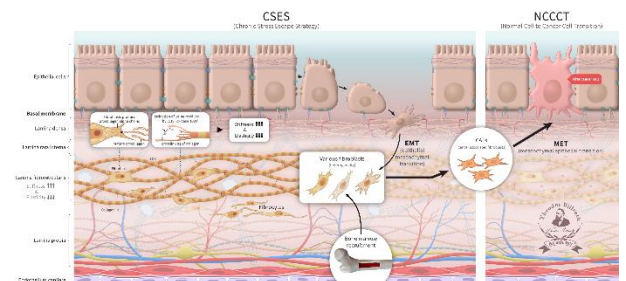
The majority of cancer (epithelial cancer) develop in response to: (1) pathogenic stimulus inducing (2) chronic inflammation, (3) fibrosis with remodeling from which a (4) pre-cancerous niche (PCN) develops.



Modified figure original published in *CELL PHYSIOL BIOCHEM* 2014, DOI 10.1159/000362978, *BMC* 2014, DOI 10.1186/1471-2407-14-331; update signaling pathways after 5 years in *4OPEN* 2019, DOI 10.1051/4OPEN/2019005.

2. Epistemology of the Origin of Cancer II (2023)

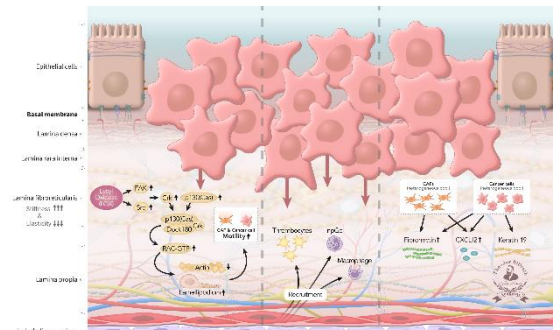
First cancer cell: (5) Chronic stress escape strategy (CSES), including EMT from epithelial cells, lead to differentiation into cancer-associated fibroblasts (CAFs), expressing epithelial & mesenchymal markers. (6) Finally, CAFs undergo MET. Epithelial marker facilitate the integration into the epithelium. Fibroblasts are the initial precursors.



Modified figure original published in *CELL PHYSIOL BIOCHEM* 2023, DOI 10.33594/000000672.

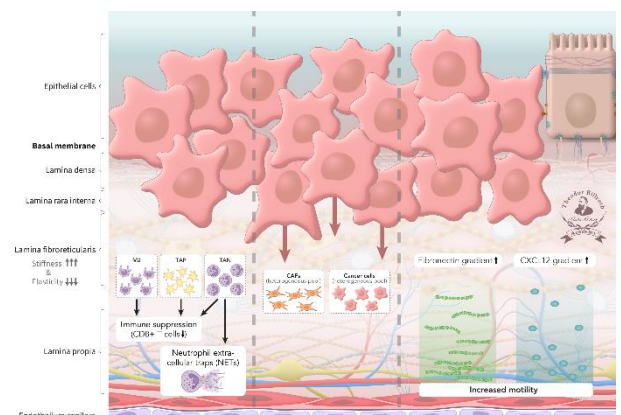
3. Epistemology of the origin of cancer III (2025)

PCN transform to metastatic niche 1 (PMN-1): Lysyl oxidase induced FAK with p130(cas)/crk/DOCK180 formation, lead to lamellipodia. CAFs & cancer cells secrete fibronectin & CXCL12, each prerequisite for rising migration. Platelets, neutrophils, and macrophages are increasingly recruited.



4. Epistemology of the origin of cancer III (2025)

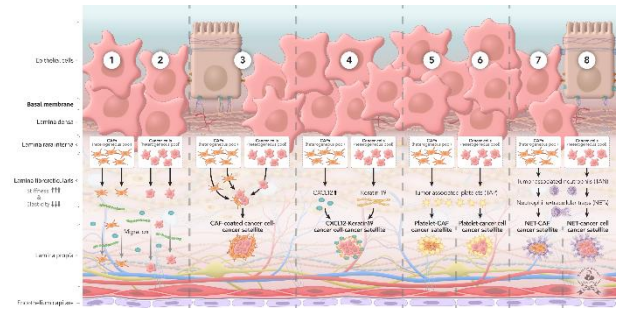
PMN-1 transformation to PMN-2: Tumor-associated cells TACs from macrophages (TAM), platelets (TAP), and neutrophils (TAN) transform from anti- to pro-tumorigenic TACs & local immunosuppression. CXCL12 and fibronectin gradient, lamellipodia, blebbing and extravesicular vesicles (EV) facilitate mobility for CAFs and cancer cells migration towards the endothelium.



5. Epistemology of the origin of cancer III (2025)

PMN-3 serves as pre-requisite that metastasis arise: 8 cancer satellites with Trojan horses enable immune escape, and disseminate.

1. Cancer cells, and
2. CAFs, migrate along CXCL12 and fibronectin gradient.
3. CAFs surround cancer cells, and migrate.
4. CXCL12–Keratin 19 coated cancer cells migrate.
5. CAFs, and
6. Platelets surround cancer cells and migrate.
7. Neutrophil formed NETs shield CAFs, and
8. Cancer cells, for migration.



Summary: Metastasis in epithelial cancer occurs in parallel with carcinogenesis after PCN is transformed into pre-metastatic niches (PMNs), which are indispensable in the origin of metastasis. A series of eight heterogeneous cancer satellites develop, including Trojan horses (immune evasion), alongside reciprocally affecting sequences, and travel alone or in combination.