

Synopsis: Special Issue on “Disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm *Epistemology of the origin of cancer*”

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Received 27 March 2018, Accepted 10 September 2019

Abstract – It is increasingly evident that carcinogenesis, in the vast majority of cancers, cannot be explained simply through an accumulation of somatic mutations, or epigenetics, the stem cell theory, or the Warburg effect. Here, decades of thinking based on incorrect assumptions has resulted in an incorrect hypothesis on the origin of cancer. Many papers studying DNA, genetics, RNA, miRNA, proteomics, and epigenetics have increased our understanding of biology. Our paradigm, though more complex, is more reliable and plausible. It states that cancer originates from a disruption of homeostasis. This essential biological phenomenon, homeostasis, maintains the interrelationships of various signaling pathways and induced crosstalk which modify cellular functions together with the interactions of surrounding cells and structures such that the equilibrium lies towards the optimal health of the organism. This Special Issue “*Disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm Epistemology of the origin of cancer*” provides compelling evidence that carcinogenesis is explained by a six-step sequence of events for the vast majority of cancers. These six steps include, (1) a pathogenic stimulus followed by (2) chronic inflammation, from which develops (3) fibrosis with associated remodeling in the cellular microenvironment. From these changes a (4) pre-cancerous niche develops which triggers the deployment of (5) a chronic stress escape strategy, and when this fails to resolve, and (6) the transition of a normal cell to a cancer cell occurs. This paradigm provides opportunities to move away from a symptom-oriented understanding of cancer and is much closer to a cause-based understanding, which opens the door for early preventative strategies to mitigate cancer as a disease, and to interdict metastases. This is underpinned by the fact that an independent recently published proof of this paradigm showed how a stimulus trigger the proposed multi-sequence cascade of events as abrupt involution-induced chronic inflammation, followed by fibrosis with remodeling, which describes the pre-cancerous niche followed by hyperplasia, metaplasia, and cancer.

Keywords: Akt, Aneuploidy, AP-2, bcl-2, BRCA, Cancer, Carcinogenesis, CD44, Cell transition, CHK2, Chronic inflammation, Crosstalk, Disruption, DNA, ECM, EGFR, Eicosanoid, Epidemiology, Epigenetics, FADS2, Fibrosis, Genetics, Genomics, GLUT-4, HBV, HCC, HCV, HETE, Homeostasis, IKK, JNK, Lipid, LOX, LOXL2, LOXL3, LTA4, LTB4, LTD4, LTE4, Lysyl oxidase, LXA4, LXB4, MaR1, MaR2, Metabolism, MicroRNA, MMP, mRNA, Microbiome, Morbid obesity, Mutation, NPD1, p16, p53, p120, Pathogenesis, PAX, PCN, PGG2, PGH2, PI3K, PPAR, Precancerous niche, Proteomics, PUFA, Radiation, Reproducibility, RvD1, RvD2, RvD3, RvD4, RvD5, RvD6, Signaling, SMT, Somatic mutation theory, SOX-2, SPM, STAT3, Stem cell, Targeting therapy, Technology, TGF, Warburg

Introduction

Cancer mortalities (e.g., breast cancer in Europe and the USA) have declined largely due to the standardization of cancer diagnosis and therapy algorithms, effective

surveillance programs, and more efficacious adjuvant therapies [1]. However, we still cannot identify the root cause (s) of cancer for some 80% of sporadic cancers as required to shift away from the current symptomatic therapies to more effective cause-based approaches.

The health-care market is well funded but the majority of these monies are spent on symptom-orientated cancer

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research. The global cancer (research and treatment) spending in 2015 was determined to be about \$100 billion [2] while the US government was spending about \$6 billion in 2018 on cancer research alone [3]. By comparison, European cancer research funding in 2012–2013 amounted ~€7.6 billion [4].

A primary suggestion to change focus in cancer research to a cause- rather than a symptom-based strategy was published between 2014 and 2016 [5–9].

Mutations, radiation, epigenetics, stem cells and Warburg theory

Mutations

Mutations that are seen in liver tissues, but not in cancer, were associated with hepatocyte regeneration independent of carcinogenesis [10]. This reveals that there is a difference between correct observations, such as mutations, and how their phenotypic diagnostic and therapeutic relevance are evaluated. Importantly, to not mistake an association as causal to cancer as has been the case for the past seven decades. In a minority of cancers, mutations do appear to be indispensable to cancer, but for example, even in the majority of BRCA mutations these appear to be biologically neutral [11]. Therefore, it becomes clearer that “mutations – regardless of cause – may not be enough, even if necessary, to cause many cancers” ([12] reviewed in [13]).

This example, among countless others, illustrates why the value of the somatic mutation theory (SMT) as being the cause for the majority of cancers is increasingly being challenged [5, 6, 9, 14–34]. It does not help if such a “holy grail” as the SMT is explained by stochastic models [35–37]. It was noted that one cannot calculate either the number of key mutations nor the susceptibility to cancer in the general population using the statistical models described [38].

It has been suggested that 20% of “healthy” adults may carry disease-related mutations and that such mutations could be identified by whole exome sequencing (WES) [39]. However, it is noteworthy that only 17% of incidental or secondary mutations identified by WES ($n = 70$) revealed that only 7.1% of the variants detected could be classified as pathogenic. Thus, there is a difference between measured observations versus a disease phenotype or a mutation that is biologically neutral [11].

The presence of somatic mutations in cancer has been extensively reviewed [9]. Investigating the expression of proteins involved in DNA repair and/or cell-cycle regulation, such as tumor protein p53 (p53), phosphorylated p53 (phosphorylated at Ser15), epidermal growth factor receptor (EGFR), ATM serine/threonine protein kinase (ATM) (phosphorylated at Ser1981) and checkpoint kinase 2 (CHK2) (phosphorylated at Thr68) showed no predictive value in esophageal squamous cell carcinoma (ESCC) [40].

It is important to note that ATM protein kinase is recruited and activated by double strand breaks in DNA [41]. Therefore, it seems to serve as a more likely explanation for the lack of predictability of disease progression or

survival from the use of biomarkers involved in DNA repair and/or cell-cycle regulation. Furthermore, extensive investigations of more common biomarkers, such as carcinoembryonic antigen (CEA) and CA199 for colon cancer show a low specificity and/or sensitivity [42] and suggests why the use of spectrometry might be of greater help in this regard [43].

The hysteron proteron syllogism “reverses both temporal and logical order and this syllogism occurs in carcinogenesis and SMT: the first (somatic mutation) occurs only after the second (onset of cancer) and, therefore, observed somatic mutations in most cancers appear well after the early cues of carcinogenesis are in place” [9]. Mutations do occur in cancerous tissue but the observed mutations and/or epigenetic and/or genetic changes in advanced cancer tissues have been consistently misinterpreted to suggest that mutations are causative for the majority of cancers. Where are the time series data that show a few mutations, then more mutations, until we see cancer develop? We consider that “somatic mutations are epiphenomena or later events occurring after carcinogenesis is already underway” [9]. The fact that a one-inch sample of cancerous liver tissue contains more than 100 million mutations [44], that identical mutations can result in different phenotypes [45], and analyses of physiologically healthy cells in the human esophagus reveal high levels of genetic alterations without cancer [46] makes it unlikely that such somatic mutations could be the cause for the vast majority of cancers [9].

It should be mentioned that even the mutation paradigm in Alzheimer’s disease (AD) was recently questioned [47] and a paradigm shift away from mutations as causal to AD was proposed [48]. It is plausible that just by random chance alone mutation-induced AD is around 5% [49] as it is for cancer [5, 9].

With regard to somatic mutations and cancers, scientists should not persist in trying to fit an opinion or belief against reliable evidence to the contrary. We need to recognize, (1) “there are larger amounts of cell-free DNA in patients with late stage disease and metastasis”, (2) the origin of the deoxyribonucleic acid (DNA) detected in fluids from cancer patients is uncertain and, so far, (3) there “is no evidence whether this DNA originates from dying “normal” cells or from cancer cells or from both” [5].

Radiation

Radiation is “the” stereotypical example in support of the primacy of mutations as being causative in cancer but a closer examination suggests that even for radiation-induced cancers a more nuanced view might be helpful. For example, the DNA damage caused by the A-bombs in Nagasaki and Hiroshima were different [9]. A low linear energy transfer (low-LET) radiation, which primarily causes single-strand DNA damage, was used in Nagasaki. Single-strand DNA damage can be repaired by DNA repair enzymes using the intact strand as a template and this explains why the dose-response curve for leukemia in Nagasaki A-bomb survivors was S-shaped, a dose-response curve which also applies for most non-carcinogenic chemicals and for pharmaceuticals ([50] reviewed in [9]). In contrast, the

ionizing radiation from the A-bomb dropped on Hiroshima was of high linear energy transfer (high-LET) type causing mostly double-strand breaks in DNA and resulting in a more linear dose-response curve. This is because in the Hiroshima survivors, the DNA repair enzymes had no template to use to repair the damaged double strand DNA ([51] reviewed in [9]). These data explain why different leukemia incidence rates were observed with different dose-response curves after the two different A-bombs in Hiroshima and Nagasaki. Children with the autosomal recessive condition, Xeroderma pigmentosum (XP), have defective DNA repair enzymes [52, 53] and illustrate why “only agents that cause double-strand DNA breakage become clinically relevant” [9].

Epigenetics

Epigenetic changes can result in hypermethylation which can silence tumor suppressor genes during carcinogenesis [8, 54, 55] as shown in gastric cancer [56, 57] and in Helicobacter-driven gastric MALT lymphomas [58].

A step-wise loss of multiple protective barriers against CpG island hypermethylation was touted as being crucial to carcinogenesis since unique epigenetic changes were observed to occur at different steps in the progression of cancers [8]. Various viruses and bacteria induce CpG island methylation [57–63]. Both hypermethylation and hypomethylation “are independent processes and appear to play different roles in colorectal tumor progression” [64].

Chronic inflammation induces promoter CpG island methylation in cancer [62, 63, 65–67]. This is significant in that our old “belief” that epigenetic alterations occur only mitotically and meiotically heritable changes is no longer correct.

Clinicians are challenged by rare small bowel adenocarcinomas (SB-AC) due to their rareness and non-specific long-standing symptoms which may explain why SB-AC present in locally advanced tumor categories [68–70]. Investigating the prevalence of hypermethylation rates in a panel of mismatch repair gene human mutL homolog 1, colon cancer, nonpolyposis type 2 (*hMLH1*), hyperplastic polyposis 1 (*HPP1*), alternate reading frame tumor suppressor protein (*p14^{ARF}*, *p14^{ARF}*), cyclin-dependent kinase inhibitor 2A, multiple tumor suppressor 1 (*p16^{INK4A}*, *p16*), and adenomatous polyposis coli (*APC*) were considered to have evolved during carcinogenesis in SB-AC with no differences in anatomical location but higher rates of *HPP1* hypermethylation in advanced tumor categories versus early tumor categories (pT1/2 categories) were observed [71]. Interestingly, male patients showed a three-fold higher *APC* hypermethylation than females. Comparing the results against gastric adenocarcinomas revealed higher rates of hypermethylation in *HPP1* and *p16^{INK4A}* in SB-AC without differences in *hMLH1* and *p14^{ARF}* suggested epigenetic differences between these tumor entities.

Subsequently, it was shown that the majority of sporadic cancers, usually diagnosed in advanced tumor categories, show more varied epigenetic alterations [72]. It remains possible, however, that methylated free-circulating DNA, such as *HPP1* DNA, might serve as an early marker

in colorectal cancer (CRC) patients who are transitioning to metastasis [73].

It has been pointed out that “we have epigenetic changes as a subset of gene regulatory changes (i.e., self-perpetuating changes) and in the older Waddington sense we could refer to all developmental gene regulation (including signaling) as “epigenetic.” But in neither case is it correct to refer to nucleosome modifiers as epigenetic” and “the important point is to attend to how things actually work” [74]. Furthermore, epigenetic changes are “important in the recruitment and regulation of the natural cellular engineering processes that are involved in DNA repair and the control of transposition and recombination” as “natural selection and natural genetic engineering overrule gene flow, evolving divergent ecological adaptive complexes” ([75] reviewed in [76]).

Paired-box genes (PAX) represent a family of transcription factors which encode proteins with DNA-binding motif and a paired domain (PD). They are classified into four major groups: group 1 (PAX1, PAX9), group 2 (PAX2, PAX5, PAX8), group 3 (PAX3, PAX7), and group 4 (PAX4, PAX6) [77–79]. After the discovery of homeobox gene by Walter Gehring ([80–82] reviewed in [83]), he discovered that PAX6 (aniridia type II protein, AN2, paired box 6) is responsible for eye development in fruit flies [84, 85]. Since then it has been shown that PAX6 has three isoforms and that it is important for embryogenesis of various tissues [86–89]. Subsequently, the potential association between PAX6 and cancer was investigated.

PAX6 is involved in normal corneal wound healing with its upregulation [90]. Otherwise, PAX6 overexpression is associated with poorer survival in invasive ductal breast cancer [91]. Increase of hypermethylation of tumor suppressing PAX6 was found to be associated with cancers of the prostate [92, 93], breast [94–97], stomach [98, 99], brain [100], and the colorectum [101]. Hepatitis C virus (HCV) positive hepatocellular carcinoma (HCC) tissue frequently (>60%) showed methylated PAX6, which rarely occurred in hepatitis B virus (HBV) positive HCC tissues [102]. Interestingly, the methylation rates of various genes are higher in HCV-HCC compared to normal tissue or HBV-HCC [103].

However, hypermethylation status should be evaluated with caution as it is necessary to know if this is found in normal tissue and we know that hypermethylation in cancer does not always involve promoter-associated CpG-islands. Moreover, methylation increases with age [8, 104, 105]. With regard to PAX6, silencing by methylation was found to be increased in tumor versus normal tissue and associated with poor survival in non-small lung cancer [106]. PAX6 overexpression increases cell migration in breast cancer, which seems to be affected by the methylation status, and increases matrix metalloproteinase 2 (MMP-2, gelatinase A) and matrix metalloproteinase 9 (MMP-9, gelatinase B), both of which are important for carcinogenesis and metastasis while the promoter methylation of PAX6 has a negative impact on cell spread and proteases expression [97].

Physical interactions between PAX6, transforming growth factor beta 1 (TGF- β 1), and secreted protein acidic

and rich in cysteine (SPARC) have been demonstrated by co-immunoprecipitation (Co-IP) assay in retinal layers but the TGF- β regulation here seems to be PAX6-dependent in a tissue-specific manner [107]. However, data in terms of the PAX6 association with various biomarkers and cancer are missing.

Stem cells

The transition from adult mesenchymal stem cells depends on homeostasis and its disruption of the extracellular matrix (ECM) with various transcription factors and cytokines ([108] reviewed in [9]). Even epithelial mesenchymal transition (EMT) itself can induce non-cancer stem cells to become stem cells ([109, 110] reviewed in [111]). “If a cancer arises in a single stem cell, then the spontaneous mutation rate would account for less than one mutation per tumor” [2]. The suggestion that “mutator phenotype” theory would explain how a large number of mutations could possibly be generated [112] was proven to be incorrect as reviewed above [11].

Warburg effect and cancer

As reviewed [113], Warburg and Cori observed that lactic acid is produced by cancer cells from the activation of anaerobic glycolysis [114–118]. To better understand how this led to a postulation that the majority of cancers would develop from anaerobic glycolysis we need to take a step back.

The metabolic physiology of oxidation goes back some 250 years [119–125]. It was the German chemist and physiologist, Max Rubner (1854–1932), who showed that food ingestion increases oxidation and is dependent on specific foods with higher rates for meat compared to fat or sugar – and it was Rubner who postulated that metabolism is directionally proportional to the surface area of the body, known as the Surface Law [126–134].

Later it was shown, that “increased acidity leads to decreased oxidation” [135]. Rabbits exposed to high carbon dioxide and normal oxygen in the atmosphere showed stimulation of the cardiorespiratory systems without bone marrow hyperplasia but with a hydropic parenchymal degeneration in some organs especially in the liver, with a more peripheral location. Low oxygen content stimulated the cardiorespiratory system together with a marked hyperplasia of red bone marrow, spleen and the thyroid together with a low rate of more central hyaline cell degeneration of parenchymatous tissue of organs and necrosis. This was concordant to prior findings [136].

Furthermore, it was assumed that vegetarians would have lower incidences of chronic diseases, such as cancer, but it was proven, that vegetarians and non-vegetarians have similar all-cause mortality including for cancer [137–139] although this seems to be dependent on the type of cancer [140, 141].

Warburg and Cori’s observations were significant to our understanding of biology. However, glycolysis is “known to be common among developing or regenerating tissues,

whether normal or neoplastic, and the tricarboxylic acid (TCA) cycle to be basically intact in neoplastic tissues” ([142] reviewed in [113]).

The above discussion suggests that the majority of cancers are unlikely to have originated from mutations, radiation, epigenetics, stem cells, or the Warburg effect.

Independent proof of cancer paradigm “Epistemology of the origin of cancer” – Complexity in animal model

A recent paper demonstrated how a pathogenic stimulus induces the multi-sequence cascade of events we proposed that includes abrupt involution-induced chronic inflammation, followed by fibrosis with remodeling, which describes the pre-cancerous niche (PCN) followed by hyperplasia, metaplasia, and cancer [143]. That this study was conducted without prior knowledge of our paradigm and without citing our previously published papers adds support for our paradigm.

Synopsis of evidence

The explanation as to how cancer cells originate is complex. It involves ubiquitous proteins [144] developing from an ongoing pathogenic stimulus with unresolved chronic inflammation [145]. This, in turn, results in fibrosis with its remodeling and generation of the PCN [146]. The PCN promotes ongoing chronic cell matrix stress resulting in the normal cell-to-cancer cell transition [111]. This sequence is influenced by the microbiome [147], its modulation by Metformin [148] as well as the metabolism of eicosanoids [149] and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling [150] all of which have been described in considerable detail in this Special Issue.

However, we acknowledge that the complexity of various sequences and specific conditions that must be considered [113].

Chronic inflammation evoked by pathogenic stimulus

The available information in regard to chronic inflammation evoked by pathogenic stimulus during carcinogenesis was extensively discussed [145] and further supported by more recent data. For example, some 25% of patients asymptomatic for benign prostatic hyperplasia (BPH) were positive for *Trichomonas vaginalis* (*T. vaginalis*) and an even higher percentage exhibited seropositivity against antibodies [151]. Thus, the findings of *T. vaginalis* in association with normal and prostatic tissues from chronic inflammatory prostatitis, BPH, and prostate cancer [152] may be more important than previously believed as one source of an ongoing pathogenic stimulus (*T. vaginalis* exposure) induces chronic inflammation within the prostate in an experimental model [153] with increases of interleukin 1 beta (IL-1 β) and chemokine (C-C motif) ligand 2 (CCL2) in a time-dependent manner leading to the transition from a normal cell to a cancer cell [154]. Chronic *T. vaginalis* infection creates the microenvironment conducive to cancer

development [155, 156]. Likewise, it has been shown that consistent chronic lung inflammation results in metaplasia and cancer [157].

This is concordant with findings on how a pathogenic stimulus in epidermal cells induces inflammation and, when unresolved, can lead to carcinogenesis [158] or to precancerous hyperplasia and endometrial cancer [159]. Even breast cancer shows such a sequence as when pathogenic stimuli, such as (HPV) type 6/11 and 16/18 infections, are followed by fibrosis with its remodeling increases the risk of such cancers [160].

Cell communication, mechanotransduction and eicosanoid metabolism

The mechanotransduction recorded in cell-cell and –stroma communication has been extensively reviewed together with the undervalued ubiquitous proteins and eicosanoid metabolism [6, 144, 149]. This alone once again supports the notion that there is no such thing as “the” and/or “one” Achilles’ Heel in cancer or carcinogenesis.

In lung cancer, the ECM protein, fibronectin, is increased and stimulated by the lipoxigenase metabolite of arachidonic acid, 12(stereoisomer)-hydroxyeicosatetraenoic acid (12(S)-HETE), but not by 12(“R” stereoisomer)-hydroxyeicosatetraenoic acid (12(R)-HETE), 5-hydroxyeicosatetraenoic acid (5-HETE) or 15-hydroxyeicosatetraenoic acid (15-HETE, (5Z,8Z,11Z,13E)-15-hydroxyicoso-5,8,11,13-tetraenoic acid) [161]. Fibronectin is increased by TGF- β 1 [162] in more aggressive cancers in the stroma but not in the tumor cells themselves [163]. Otherwise, fibronectin was reported in the 80s as not being a useful marker as it was not increased in cancer cells [164]. It should be noted that the cancer cells were the focus of studies in the 80s and beginning of the 90s, not the stroma, which explains why the role of fibronectin was previously undervalued.

Fibronectin protects lung cancer cells against chemotherapy induced apoptosis [165]. Culturing human ovarian cancer cells (OVCAR-3, A2780/CP70) with fibronectin increases signaling regulation of the focal adhesion kinase (FAK) pathway (phosphorylated phosphoinositide 3-kinase (pPI3K)/phosphorylated phosphorylated protein kinase B (pAKT) with the ability to migrate and invade tissue which can be inhibited by FAK siRNA [166]: fibronectin plays a role in metastasis as well.

Cluster of differentiation 44 (CD44) is increased by pathogenic stimulus in carcinogenesis and also increased by chronic TGF- β 1 [111]. Targeting glioblastoma cells expressing CD44 with liposomes encapsulating doxorubicin was reported to suppress tumor growth [167]. CD44 induces integrin-mediated signaling for increasing adhesion to facilitate extravasation and increases adhesion to fibronectin which enables cancer cells to adhere more efficiently [168]. Therefore, it is currently thought that targeting fibronectin may be helpful in cancer therapy and also in cancer imaging [169].

Focal adhesion kinase (FAK) and the protein, paxillin, promote migration and adhesion to fibronectin [170]. Paxillin is increased in various lesions, such as hyperplasia,

dysplasia, metaplasia, and cancers [171] and connects integrin to FAK [172].

PAX6 is under investigation in embryogenesis [86–89, 173, 174]. However, transcription factors can be differently expressed viz., neuroblasts in the human subventricular zone showed increased Sox-2 expression in the nuclear region, whereas PAX6 immunoreactivity was detectable in both the nucleus and the cytoplasm [175]. The cell adhesion integral membrane molecule, L1, consists of six Ig domains together with five fibronectin types, three repeats, and a cytoplasmic domain [176]. Here a binding site for homeodomain and PAX proteins is necessary for L1 adhesion [177].

More detailed mechanistic information was recently provided for PAX6: the transcription factor PAX6 binds on zinc finger E-box-binding homeobox 2 (ZEB2) and upregulates PI3K/Akt signaling with E-Cadherin decrease down-regulating apoptosis in lung cancer [178]. Detailed information about lysyl oxidase (LOX), or its isoforms, with PAX6 signaling are warranted. PAX6 was shown to increase MMP-2 and MMP-9 [97], both of which are important for the degradation and destruction of the ECM [9]. Furthermore, co-expression of PAX6 and C-X-C chemokine receptor 4 (CXCR4) was shown in pancreatic cancer [179], although here the mechanistic interactions are presently not known.

Fibrosis with its remodeling and generation of the precancerous niche (PCN)

Inducing the precancerous niche (PCN) in its entirety reveals how carcinogenesis can occur [146]. In this context, the influence by the microbiome and obesity, and the role of Metformin are discussed [147] along with the different influences by various NF- κ B signaling pathways [150] which all have been reviewed extensively. New reports suggest that Metformin can reverse the mesenchymal phenotype of primary breast cancer cells through signal transducer and activator of transcription 3 (STAT3)/NF- κ B pathways [180].

As reported [146], the copper-dependent amine oxidases of the LOX its isoforms and receptors, together with the study of cancer-resistant species such as the naked mole rat or Spalax are relevant. The LOX family consists of LOX, lysyl oxidase-like protein 1–4 (LOXL1, LOXL2, LOXL3, and LOXL4) and these are important for ECM stiffness, stabilization [181], as well as for its remodeling with altered signaling during carcinogenesis [146]. LOX have a pivotal role in TGF- β 1-induced carcinogenesis as well as in cutaneous fibrosis through impaired ECM homeostasis in skin-like tissues [182].

LOXL3 is key regulator of integrin signaling and known to oxidize fibronectin to augment the signal transduction adaptor protein, phosphorylated Paxillin, which appears to be an essential step for matrix formation [183].

The extracellular LOXL3 is expressed in the cytoplasm in melanoma and kidney cells ([184, 185] reviewed in [181]) but predominantly translocated to the nucleus as was observed in gastric cancer ([186] reviewed in [181]).

It may be relevant that LOXL3 in humans presents “*potential transcription factor binding sites for STAT3, signal transducer and activator of transcription 6 (STAT6), serum response factor (SRF) muscle integrin binding protein (MIBP)/regulatory factor X1 (RFX1), specificity protein 1 (SP1), nuclear factor 1 (NF1), neuron-restrictive silencer factor (NRSF, RE1-silencing transcription factor, REST), cAMP response element (CRE)-binding protein 1 (CREB), PAX-6 paired domain, interferon regulatory factor (IRF)-related protein, GATA binding factor 1, NF- κ B, GAGA box, proto-oncogene c-Rel (c-Rel) sites, and activating protein 2 (AP-2)*” ([187] reviewed in [181]).

Chronic cell matrix stress resulting in the normal-to-cancer cell transition

“*In biology, the transition of one cell type to another and the transition from one cell function to another is incompletely understood mechanistically, but within the context of embryogenesis and morphogenesis is acknowledged as a physiologically routine event*” [111]. Catenin delta-1 (p120) regulates lung fibroblast differentiation induced by TGF- β 1 [188]. Chronic cell matrix stress increases p120 within the cytoplasm, and destabilizes epithelial cadherin 1 (E-Cadherin, CAM 120/80), which explains why apoptosis is inhibited under these conditions [189, 190]. A central role for p120 in chronic cell stress response was also shown in drosophila [191]. However, p120 and its isoforms 1 and 3 (p120-1 and p120-3) are differently expressed in epithelial tissues [192].

During carcinogenesis, the disruption of p120 homeostasis is relevant as p120 isoform 1 promotes transition cell invasiveness while isoform 3 inhibits both [193] which makes it more complex as the effects of p120 depend on its isoforms. The obstacle of cell transition increases that complexity as intermediate cell states have been identified [194]. Although there is hope that influencing cell transition could be used in treating disease [195], much work needs to be done to first fill in the gaps in our knowledge.

We acknowledge the complexity illustrated by lipid metabolism as discussed below.

Disruption of lipid metabolism

The homeostasis of pro- and anti-inflammatory effects during carcinogenesis is disrupted in multiple ways, which reveal why the focus on any one signaling pathway will not suffice to interrupt carcinogenesis.

One important aspect lies in fatty acid metabolism which results in various intra- and extracellular mediators [149] with pro-inflammatory effects, such as prostaglandins, such as prostaglandin G2 (PGG2, (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) and prostaglandin H2 (PGH2, (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, leukotrienes (LTs), such as leukotriene A4 (LTA4, 4-[(2S,3S)-3-[(1E,3E,5Z,8Z)-tetradeca-1,3,5,8-tetraenyl]oxiran-2-yl]butanoic acid), leukotriene B4 (LTB4, (5S,6Z,8E,10E,

12R,14Z)-5,12-dihydroxyicosa-6,8,10,14-tetraenoic acid), leukotriene C4 (LTC4, (5S,6R,7E,9E, 11Z, 14Z)-6-[(2R)-2-[[[(4S)-4-amino-4-carboxybutanoyl]amino]3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid), leukotriene E4 (LTE4, (5S,6R,7E,9E, 11Z,14Z)-6-[(2R)-2-amino-2-carboxyethyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid), leukotriene D4 (LTD4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid) and anti-inflammatory specialized pro-resolving lipid mediators (SPMs), such as lipoxines (LXs), such as lipoxin A4 (LXA4, 5S,6R,15S-trihydroxy-7E,9E, 11Z,13E-eicosatetraenoic acid), lipoxin B4 (LXB4, 5S, 14R,15S-trihydroxy-6E,8Z,10E,12E-eicosatetraenoic acid), resolvins (RVs), such as resolvin D1 (RvD1, (4Z,7S,8R, 9E,11E,13Z,15E,17S, 19Z)-7,8,17-trihydroxydocosa-4,9,11, 13,15,19-hexaenoic acid), resolvin D2 (RvD2, (4Z,7S,8E, 10Z,12E,14E, 16R,17S,19Z)-7,16,17-trihydroxydocosa-4,8,10, 12,14,19-hexaenoic acid), resolvin D3 (RvD3, (4S,5E, 7E,9E,13Z, 15E,17R,19Z)-4,11,17-trihydroxydocosa-5,7,9,13, 15,19-hexaenoic acid), resolvin D4 (RvD4, (4S,6E,8E, 10E, 13E,15Z,17S,19Z)-4,5,17-trihydroxydocosa-6,8,10,13,15, 19-hexaenoic acid), resolvin D5 (RvD5, (5Z,7S,8E,10Z,13Z, 15E,17S,19Z)-7,17-dihydroxydocosa-5,8,10,13,15,19-hexaenoic acid), and resolvin D6 (RvD6, (4S,5E,7Z, 10Z,13Z, 15E,17S,19Z)-4,17-dihydroxydocosa-5,7,10,13,15, 19-hexaenoic acid), such as neuroprotectin D1 (NPD1, protectin D1, (4Z,7Z,10R,11E,13E,15Z,17S,19Z)-10,17-dihydroxydocosa-4,7,11,13,15,19-hexaenoic acid), and maresins, such as maresin 1 (MaR1, (4Z,7R,8E,10E,12Z,14S, 16Z,19Z)-7,14-dihydroxydocosa-4,8,10,12,16,19-hexaenoic acid) and maresin 2 (MaR2, 13R,14S-diHDHA).

Noticeable within fatty acid (FA) metabolism is the homeostasis between synthesis in the cytoplasm and the endoplasmic reticulum in humans (and plastids in plants) while FA degradation takes place within the mitochondria, peroxisomes, and glyoxosomes [196–201].

Humans consume predominantly six common edible saturated FA, such as hexadecanoic acid (*palmitic acid*), (9Z)-hexadec-9-enoic acid (*palmitoleic acid*), octadecanoic acid (*stearic acid*, cetylacetic acid), cis-9-octadecenoic acid (*oleic acid*), linoleic acid (LA, cis, cis-9,12-octadecadienoic acid) and α -linolenic acid (ALA, (9Z,12Z,15Z)-octadeca-9,12,15-trienoic acid) [149, 202, 203].

Fatty acid precursors such as ALA are converted to the more pro-inflammatory *n*-6 polyunsaturated fatty acid (***omega-6-*, ω -6-PUFAs**: C20H32O2, 20:4(ω -6)), such as dihomo gamma-linolenic acid (*DGLA*), arachidonic acid (*AA*), docosatetraenoic acid, (7Z,10Z,13Z,16Z)-7,10,13, 16-docosatetraenoic acid (*DTA*) and osbond acid, (All-Z)-4,7,10,13,16-docosapentaenoic acid (*BDPA*), and through LA into the less inflammatory *n*-3 polyunsaturated fatty acids (***omega-3-*, ω -3-PUFAs**), such as 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*).

Key reaction in biosynthesis of PUFA is desaturation [203–205]. Enzymes transfer electrons from one molecule to another and desaturate the substrate by adding a double bond. FA with double bonds are essential and need to be ingested in food because specialized desaturases are missing. So-called Δ -desaturases are classified in regard to the double bond position counting from the methyl end, e.g. delta-9, delta-6 and delta-5 types ([206, 207] reviewed in [208]).

In the following we *will not* focus on the bacterial desaturase (DesA), cyanobacterial DesA, which is important for cooling tolerance. Lipid membranes are temperature-dependent based on the grade of saturation [209] and specialized FA can generate an increased tolerance against cold temperatures in higher plants [210]. Instead we will focus on stearoyl-CoA desaturase-1 (SCD1) and fatty acid desaturase 2 (FADS2).

Stearoyl-CoA desaturase-1 (SCD1) = Δ -9 desaturase (D9D)

Stearoyl-CoA desaturase-1 (SCD1) [206, 211–214] is a Δ -9 desaturase (D9D). SCD1 is essential for the de-novo triglyceride biosynthesis [215]. Mono-unsaturated fatty acids (MUFA), such as oleic acid and palmitoleic acid are substrates for various lipid syntheses, such as triglycerides (TGs), wax esters, cholesterol esters and phospholipids. In importance, next to various cell communication molecular pathways [6, 149] is the ratio of saturated to unsaturated FA in the phospholipids as this influences the stability and fluidity of membranes and thus influences signal transduction [216]. SCD1-expression influences the membrane phospholipid composition.

SCD1-deficiency is associated with reduced obesity and decreased liver steatosis independent of peroxisome proliferator-activated receptor- α (PPAR α) [217]. Deficiency of SCD1 also results in reduced arteriosclerosis [218], adiposity [217, 219], adipose tissue associated inflammation [220, 221] inhibits glycogen synthase kinase 3 (GSK3) phosphorylation, and decreases β -catenin translocation to the nucleus with consecutive decrease of cell proliferation and cell transition in breast cancer cells [222]. Therefore, SCD1 inhibitors hold the promise of being targets in anticancer therapy [223].

The mediator of increased hepatic FA oxidation in SCD1-deficiency is the phosphorylation and activation of AMP-activated protein kinase (AMPK) which act like a metabolic sensors [224]. Pharmacological SCD1 inhibition inactivates acetyl-CoA carboxylase via AMPK and impairs proliferation in lung cancer cells [225]. SCD1 is positively regulated by insulin [226] and vitamin A [227] and suppressed by triiodothyronine (T3) [228]. In obesity, leptin decreases SCD1-independent of insulin [229] and insulin activates SCD1 expression through PI3K and the mechanistic target of rapamycin (mTOR) as well as the downstream transcription factors nuclear factor Y (NF-Y) and sterol regulatory element-binding protein 1 (SREBP-1) [230].

PI3K/mTOR signaling upregulates SCD1 [231–233]. Furthermore, EGFR binds and phosphorylates SCD1 and

cancer cell growth stimulated by EGFR depends on SCD1 activity [234]. SCD1 controls cancer metabolism as well as proliferation and cell-survival through EGFR/Akt/extracellular signal-regulated kinase (ERK) signaling [235]. SCD1 decreases apoptosis, increases proliferation, and metastasis-related EGFR/PI3K/Akt signaling plus up-regulation of epithelial to mesenchymal transition (EMT) phenotype in lung cancer, which could be restored by SCD1 inhibition. In this case, SCD1 inhibition is required for anti-EGFR therapy in lung cancer [236].

NF- κ B [150] upregulates SCD1 at the transcriptional level [237]. SCD1 inhibition also blocks NF- κ B signaling and downregulates interleukin 6 (IL-6) but the exact signaling pathway remains to be elucidated. Furthermore, the degree of disruption of homeostasis is important as only moderate activation of inhibitor of nuclear factor kappa-B kinase subunit beta, IKK- β -NF- κ B in unstressed adult mouse liver cells seems to induce lipogenesis and to be cytoprotective without apparent inflammation and fibrosis [238]. This appears to be related to the strong activation of the anti-inflammatory IKK1-RelB alternative NF- κ B pathway. Knockdown of SCD1 by shRNA reduced the mRNA expression of aldehyde dehydrogenase 1 family member A1 (ALDH1A1), the homeobox protein Nanog, sex determining region Y (SRY)-box 2 (Sox2), and octamer-binding transcription factor 4 (Oct-4) [237].

Angiotensin II (ANGII) promotes the formation of multicellular spheroids (MCS) and peritoneal metastasis through EGFR transactivation and activation of its receptor, angiotensin II receptor type 1 (AGTR1, AT₁-receptor), increases the lipid desaturation via SCD1 upregulation explaining why high AGTR1 levels are associated with poor outcomes in ovarian cancer [239].

Cancer cells usually have a much higher proliferation rate than normal cells and require a higher proportion of PUFA for their cell membranes as well as for the formation and stabilization of cell membranes ([240] reviewed in [241]). Fibroblasts [242] and SV40-triggered transformed fibroblasts upregulate SCD1 [243].

Increased SCD1 is associated with cancers and cell lines of the breast [244, 245], ovarian [246], hypopharynx [240], thyroid [247], esophagus [248], colon [248–250], liver [248, 251, 252], the lung [241, 253–255], kidney [256], and the prostate [257] as well as in melanoma [258].

Sapienate and fatty acid desaturase 2 (FADS2) = Δ -6-desaturase (D6D) (Fig. 1)

The unique and abundant MUFA, sapienic acid (sapienate) is the most abundant FA in human sebum and among hair-bearing animals ([259] reviewed in [260]). Sapienate is an intermediate product of saturated palmitate to cis-8-octadecenoate [261]. FADS2 is a Δ -6-desaturase (D6D) [260, 262–264] and was identified in human sebaceous glands where it converts palmitate into the MUFA, sapienate [260].

More recently it was shown that FADS2 signaling is used by cancer cells to produce sapienate as an alternate

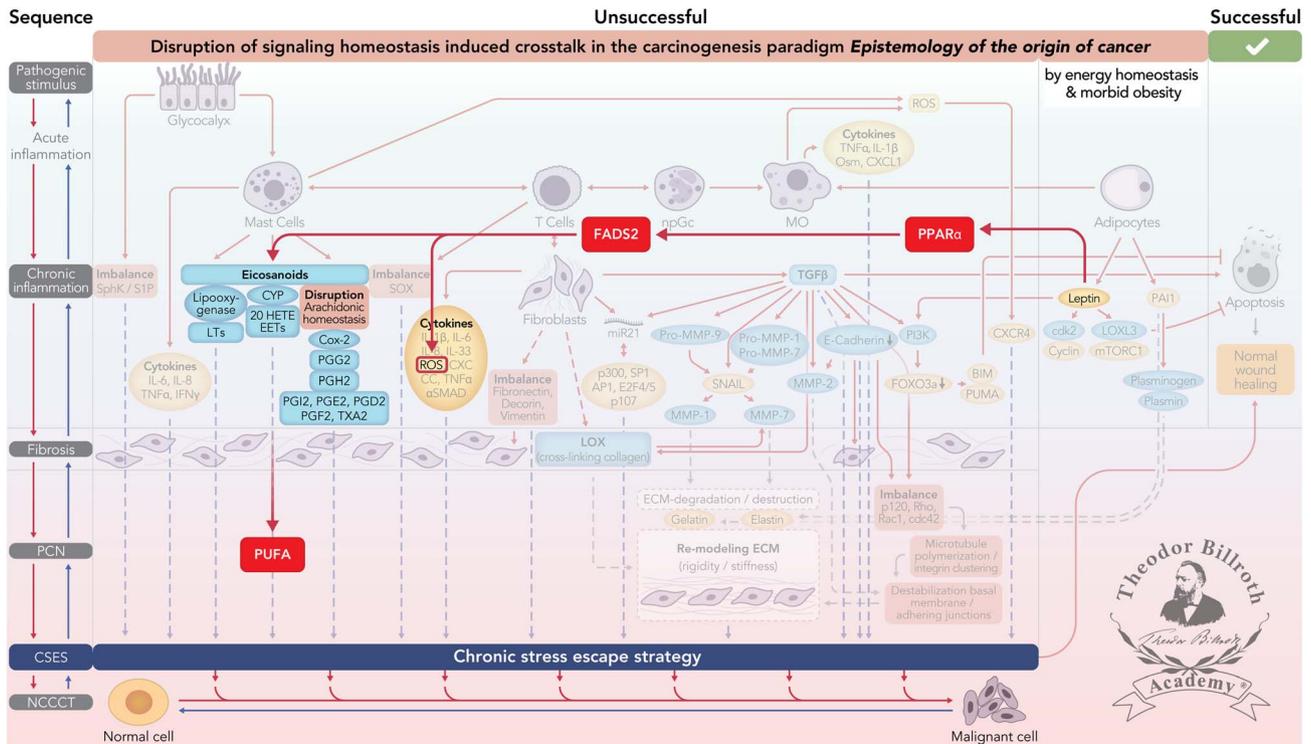


Figure 1. Simplified scheme of fatty acid desaturase 2 (FADS2) = ω -6-desaturase (D6D) signaling in the disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm “*Epistemology of the origin of cancer*” consisting of a six-step sequence (1) a pathogenic stimulus followed by (2) chronic inflammation from which develops (3) fibrosis with associated remodeling of the cellular microenvironment; and from these changes a (4) precancerous niche (PCN), a product of fibrosis, with remodeling by persistent inflammation, develops which triggers the deployment of (5) a chronic stress escape strategy and when this fails resolve it by (6) normal cell to cancerous cell transition (NCCCT) by PCN-induced cell matrix stress occurs. This figure was published as original illustration in paper 3 of this Special Issue – Disruption of homeostasis-induced signaling and crosstalk in the carcinogenesis paradigm “*Epistemology of the origin of cancer*” entitled “*Chronic inflammation evoked by pathogenic stimulus during carcinogenesis*” [145]. Furthermore, we point out, that to the complexity of the content of the Special Issue the original and/or modified version of the original illustration was republished within the following papers of the Special Issue: paper 5 “*Microbiome and morbid obesity increase pathogenic stimulus diversity*” [147], paper 6 “*Precancerous niche (PCN), a product of fibrosis with remodeling by incessant chronic inflammation*” [146], paper 7 “*Metformin alters signaling homeostasis*” [148], paper 8 “*Transition from normal to cancerous cell by precancerous niche (PCN) induced chronic cell-matrix stress*” [111] and paper 9 “*NF- κ B signaling and crosstalk during carcinogenesis*” [150]. *Nomenclature Figure 1:* The nomenclature common abbreviations are bold, followed by the common trivial names (if available) and (if available) by the name in accordance to the International Union of Pure and Applied Chemistry (IUPAC): **FADS2**: fatty acid desaturase 2, = ω -6-desaturase (D6D); **PPAR α** : peroxisome proliferator-activated receptor- α ; **PUFA**: polyunsaturated fatty acids; **PCN**: precancerous niche; **CSES**: chronic stress escape strategy; **NCCCT**: normal cell to cancerous cell transition; **SphK**: sphingosine kinase isoform; **S1P**: sphingosine-1-phosphate; **IL-6**: interleukin 6; **IL-8**: interleukin 8; **TNF α** : tumor necrosis factor α ; **IFN γ** : interferon gamma; **ALOX**: lipoxygenase, arachidonate lipoxygenase; **ALOX12**: 12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type; **ALOX5**: 5-lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase; **12-HETE**: 12-hydroxyeicosatetraenoic acid; **LTA4**: leukotriene A4, 4-[(2S,3S)-3-[(1E,3E,5Z,8Z)-tetradeca-1,3,5,8-tetraenyl]oxiran-2-yl]butanoic acid; **LTB4**: leukotriene B4, (5S,6Z,8E,10E,12R,14Z)-5,12-dihydroxyicosa-6,8,10,14-tetraenoic acid; **LTC4**: leukotriene C4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-[[4S)-4-amino-4-carboxybutanoyl]amino]-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid; **LTD4**: leukotriene D4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid; **LTE4**: leukotriene E4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-2-carboxyethyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid; **5-oxo-ETE**: (6E,8Z,11Z,14Z)-5-oxoicosa-6,8,11,14-tetraenoic acid; **Cox**: cyclooxygenase; **Cox-1**: cyclooxygenase 1; **Cox-2**: cyclooxygenase 2; **Cox-3**: isoform of Cox-2 (therefore in brackets); **PGG2**: prostaglandin G2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroperoxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; **PGH2**: prostaglandin H2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; **PGFF2 α** : prostaglandin F2 α , (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid; **PGD2**: prostaglandin D2, (Z)-7-[(1R,2R,5S)-5-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid; **PGE2**: prostaglandin E2, (Z)-7-[(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid; **MDA**: malondialdehyde, propanedial; **TXA2**: thromboxane A2, (Z)-7-[(1S,2S,3R,5S)-3-[(E,3S)-3-hydroxyoct-1-enyl]-4,6-dioxabicyclo[3.1.1]heptan-2-yl]hept-5-enoic acid; **CYP***: cytochrome P450 isoforms; **20-OH-PGE2**: 20-hydroxy prostaglandin E2; **20-HETE**:

metabolic pathway which the cells (ab)use it for membrane synthesis of cancer cells [265]. In accordance with a Figure published in this Special Issue [145], the FADS2 signaling fits in well with the thinking detailed in this Special Issue (Fig. 1).

Transcriptional coactivator yes-associated protein (YAP) (Fig. 2)

Another recent publication used heat maps generated by RNA transcriptomes and green fluorescent protein-labeled (GFP+) B16F10 marked melanoma cells for metabolomic analysis. This study revealed that cancer cells use the production of bile acids in lymph node metastasis and a metabolic shift through transcriptional coactivator, yes-associated protein (YAP), as a mechanism to spread through lymph nodes [266]. It was shown, that inhibiting mammalian target of rapamycin complex 1 (mTORC1) results in the inhibition of YAP and its transcriptional coactivator with PDZ-binding motif (TAZ)-mediated liver cancer development [267]. Also, as shown in a figure published in this Special Issue [145], the YAP signaling fits well into our overall thought process discussed in this Special Issue (Fig. 2). Here, YAP can have ambivalent effects on apoptosis [268, 269].

A challenge in the future of science and cancer research will be using new technologies to develop specific anticancer therapies, which are not going to be easy as widely portrayed because of the need to integrate multi-sequence strategies to mitigate the disruption of homeostasis.

Scope of new technologies

There is an expectation that imaging at the molecular and atomic levels will provide new insights into cancer. The identification of virus particles at the atomic level, decoded by X-ray laser, was recently reported for the first time [270]. Imaging correction and enhancement by software of time-lapse microscopy will make previously hidden developmental steps in cells visible in time [271]. Magnetic nanoparticle magnetic resonance imaging (MRI) using ferumoxytol non-invasively visualized pancreatic inflammation in Type-1 diabetics [272] and nanomedicine technology might be a reliable tool to better understand physicochemical characteristics for use in the development

of cancer pharmaceuticals [273]. Future mRNA imaging might also provide information for visualizing biochemical reactions which may create new opportunities for research [274]. For instance, such imaging tools might provide for a deeper understanding of our immune system and its interplay with various cell types, cytokines, and biochemical signaling.

The following signaling and crosstalk pathways might be elucidated using nano-imaging: immune cells promote activation and nuclear localization of inhibitor of nuclear factor kappa-B kinase 1 (IKK1, inhibitor of nuclear factor kappa-B kinase subunit alpha, IKK- α) in prostatic epithelial tumor cells which can result into the suppression of maspin leading to metastasis [275, 276].

N-methyl-D-aspartate receptors (NMDA) are glutamate-gated cation channels with high calcium permeability playing roles in the biology of higher organisms [277]. Inhibiting NMDA by dextromethorphan (DXM) was shown to result in enhanced serum insulin concentrations and improved glucose tolerance [278]. The NF- κ B signaling and its influence by Metformin has been reviewed [150, 180]. A better and more complete understanding of Metformin's role in crosstalk pathways in diabetes could result in potential therapeutic use of Metformin against specific targets in certain cancers.

Pharmacological modulators of cation (calcium, sodium, potassium) and anion-permeable channels might impact cancer treatments [279] and pharmacogenomics might help further optimize patient sub-selection so as to better predict responses to cancer therapy [280].

The theory suggested to engineer gene-driven systems by Burt [281] and the discovery of the bacterial nuclease system named clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) [282] resulted in the false hope that cut-and-paste of any DNA sequence might cure any and all mutation-caused disease. As a cautionary tale, Chamber et al. revealed that rapid resistance to CRISPR gene engineering occurs, often in a single generation [283]. The editorial of the Journal was titled "*The gene drive bubble: New realities*" [284] to remind the scientific community about the necessity that such new technologies should be used with an abundance of caution and with realistic expectations of what they can and cannot deliver.



Figure 1. (continued) 20-hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,14Z)-20-hydroxyicosa-5,8,11,14-tetraenoic acid; **SOX**: [sex-determining region Y (Sry) box-containing] transcription factor family; **IL- β 1**: interleukin beta 1; **IL-33**: interleukin 33; **ROS**: reactive oxygen species; **CXC CC**: chemokine receptors; **α SMAD**: alpha-smooth muscle actin; **miR21**: micro RNA-21; **p300**: protein 300 (p300-CBP coactivator family); **SP1**: specificity protein 1; **AP1**: activator protein 1; **E2F4/5**: cytoplasmic complex of Smad3, retinoblastoma-like protein 1 (P107, RBL1), E2F4/5 and D-prostanoid (DP1); **p107**: retinoblastoma-like protein 1, RBL1; **TGF β** : transforming growth factor beta; **Pro-MMP-9**: pro-matrix metalloproteinase 9; **Pro-MMP-1**: pro-matrix metalloproteinase 1; **Pro-MMP-7**: pro matrix metalloproteinase 7; **SNAIL**: zinc finger protein SNAI1; **MMP-1**: matrix metalloproteinase 1; **MMP-7**: matrix metalloproteinase 7; **MMP-2**: matrix metalloproteinase 2; **E-Cadherin**: CAM 120/80 or epithelial cadherin, cadherin-1, epithelial cadherin; **CXCL1**: chemokine (C-X-C motif) ligand 1; **Osm**: oncostatin-M; **PI3K**: phosphatidylinositol 3-kinase; **FOXO3a**: forkhead box protein O3a; **p120**: catenin delta-1, protein 120; **Rho**: Ras homolog gene family, member A; **Rac1**: Ras-related C3 botulinum toxin substrate 1; **cdc42**: cell division control protein 42 homolog; **BIM**: Bcl-2 interacting mediator of cell death; **PUMA**: BH3-only protein; **CXCR4**: C-X-C motif of chemokine receptor 4; **cdk2**: cyclin-dependent kinase 2; **LOXL3**: lysyl oxidase homolog 3; **mTORc1**: rapamycin complex 1; **PAI1**: Plasminogen activator inhibitor-1.

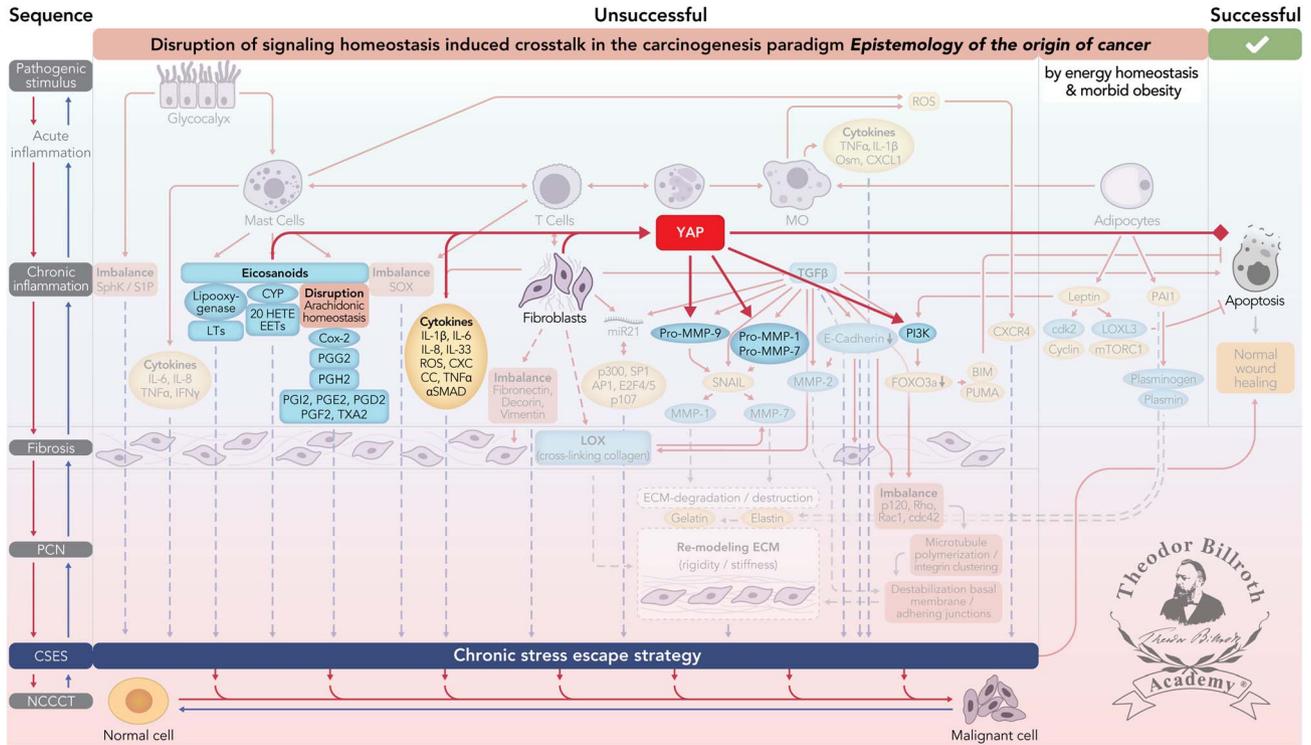


Figure 2. Simplified scheme of transcriptional coactivator yes-associated protein (YAP) signaling in the disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm “*Epistemology of the origin of cancer*” consisting of a six-step sequence (1) a pathogenic stimulus followed by (2) chronic inflammation from which develops (3) fibrosis with associated remodeling of the cellular microenvironment; and from these changes a (4) precancerous niche (PCN), a product of fibrosis, with remodeling by persistent inflammation, develops which triggers the deployment of (5) a chronic stress escape strategy and when this fails resolve it by (6) normal cell to cancerous cell transition (NCCCT) by PCN-induced cell matrix stress occurs. This figure was published as original illustration in paper 3 of this Special Issue – Disruption of homeostasis-induced signaling and crosstalk in the carcinogenesis paradigm “*Epistemology of the origin of cancer*” entitled “*Chronic inflammation evoked by pathogenic stimulus during carcinogenesis*” [145] [Chronic inflammation 4open 2019]. Furthermore, we point out, that to the complexity of the content of the Special Issue the original and/or modified version of the original illustration was republished within the following papers of the Special Issue: paper 5 “*Microbiome and morbid obesity increase pathogenic stimulus diversity*” [147], paper 6 “*Precancerous niche (PCN), a product of fibrosis with remodeling by incessant chronic inflammation*” [146], paper 7 “*Metformin alters signaling homeostasis*” [148], paper 8 “*Transition from normal to cancerous cell by precancerous niche (PCN) induced chronic cell-matrix stress*” [111] and paper 9 “*NF-kB signaling and crosstalk during carcinogenesis*” [150]. Here, YAP can have ambivalent effects on apoptosis [268, 269] why the connection between YAP and apoptosis ends at the stroke within the illustration with a rhombus. *Nomenclature Figure 2:* The nomenclature common abbreviations are bold, followed by the common trivial names (if available) and (if available) by the name in accordance to the International Union of Pure and Applied Chemistry (IUPAC): **YAP**: yes-associated protein; **PCN**: precancerous niche; **CSES**: chronic stress escape strategy; **NCCCT**: normal cell to cancerous cell transition; **SphK**: sphingosine kinase isoform; **S1P**: sphingosine-1-phosphate; **IL-6**: interleukin 6; **IL-8**: interleukin 8; **TNF α** : tumor necrosis factor alpha; **IFN γ** : interferon gamma; **ALOX**: lipoxygenase, arachidonate lipoxygenase; **ALOX12**: 12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type; **ALOX5**: 5-lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase; **12-HETE**: 12-hydroxyeicosatetraenoic acid; **LTA4**: leukotriene A4, 4-[(2S,3S)-3-[(1E,3E,5Z,8Z)-tetradeca-1,3,5,8-tetraenyl]oxiran-2-yl]butanoic acid; **LTB4**: leukotriene B4, (5S,6Z,8E,10E,12R,14Z)-5,12-dihydroxyicoso-6,8,10,14-tetraenoic acid; **LTC4**: leukotriene C4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-[[[(4S)-4-amino-4-carboxybutanoyl]amino]-3-(carboxymethylamino)-3-oxopropyl]sulfonyl-5-hydroxyicoso-7,9,11,14-tetraenoic acid; **LTD4**: leukotriene D4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-3-(carboxymethylamino)-3-oxopropyl]sulfonyl-5-hydroxyicoso-7,9,11,14-tetraenoic acid; **LTE4**: leukotriene E4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-2-carboxyethyl]sulfonyl-5-hydroxyicoso-7,9,11,14-tetraenoic acid; **5-oxo-EETE**: (6E,8Z,11Z,14Z)-5-oxoicoso-6,8,11,14-tetraenoic acid; **Cox**: cyclooxygenase; **Cox-1**: cyclooxygenase 1; **Cox-2**: cyclooxygenase 2; **Cox-3**: isoform of Cox-2 (therefore in brakes); **PGG2**: prostaglandin G2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroperoxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; **PGH2**: prostaglandin H2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; **PGFF2 α** : prostaglandin F2 alpha, (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid; **PGD2**: prostaglandin D2, (Z)-7-[(1R,2R,5S)-5-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid; **PGE2**: prostaglandin E2, (Z)-7-[(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid; **MDA**: malondialdehyde, propane-dial; **TXA2**: thromboxane A2, (Z)-7-[(1S,2S,3R,5S)-3-[(E,3S)-3-hydroxyoct-1-enyl]-4,6-dioxabicyclo[3.1.1]heptan-2-yl]hept-5-enoic acid; **CYP***: cytochrome P450 isoforms; **20-OH-PGE2**: 20-hydroxy prostaglandin E2; **20-HETE**: 20-hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,14Z)-20-hydroxyicoso-5,8,11,14-tetraenoic acid; **SOX**: [sex-determining region Y (Sry) box-containing] transcription factor family; **IL- β 1**: interleukin beta 1; **IL-33**: interleukin 33; **ROS**: reactive oxygen species; **CXC CC**: chemokine receptors;

Developing targeted therapy not as easy as advertised

Tacrolimus (FK506) binding protein 5 (FKBP51) is a 51 kDa chaperon molecule and an endogenous cytosolic peptidyl-prolyl isomerase counted among the immunophilin protein family [285, 286] with others [287, 288]. Immunophilins had been described as receptor molecules for immunosuppressive drugs, such as cyclophilin 40 (CyP40), FK506-binding proteins FKBP51 and FK506-binding protein 4 (FKBP52), protein phosphatase 5 (PP5), and heat shock protein 90 (Hsp90) [289]. Its involvement in various signaling pathways and in diseases is incompletely understood at present but there is hope that an anti-FKBP51 targeted therapy could be helpful for some diseases [290] but would need to be evaluated carefully in terms of potential effects on the signaling pathways in carcinogenesis because potential secondary adverse signaling effects could be created.

FKBP51 is associated with autophagy, psychiatric disorders, and diabetes. Experiments with cultured cells and FKBP51 knockdown mice showed that FKBP51 is involved in priming autophagy signaling and intracellular complexes and is actively required for setting the groundwork for antidepressants to work on the brain as evidenced by the observation that lacking FKBP51 in a mouse model abolished the antidepressant effects [291]. FKBP51 is associated with diabetes as it antagonizes the increase of phosphorylation of Akt substrate of 160 kDa (AS160), glucose transporter type 4 (GLUT-4) expressions at the plasma membrane, and glucose uptake in skeletal myotubes [292]. Blocking FKBP51 could result in reducing or preventing diabetes as decreased FKBP51 levels are associated with reduced glucose intolerance and with maintaining or restoring metabolic homeostasis.

Anti-FKBP51 targeting can also cause unwanted adverse effects. The role of glycogen synthase kinase 3 β (GSK-3 β) in carcinogenesis has been previously reviewed [146]. Inhibiting GSK-3 β in glioblastoma cells is associated with induction of apoptosis and decrease of cell proliferation in vitro and in vivo [293]. However, there is a potential FKBP51/GSK-3 β interaction in cancer. FKBP51 increases the phosphorylation of GSK-3 β at serine 9 (pGSK-3 β S9) through its FK1 domain and also modifies GSK-3 β 's heterocomplex formation via protein phosphatase 2 (PP2, PP2A) and

the cyclin-dependent kinase 5 (cell division protein kinase 5, CDK5) resulting in the inhibition of GSK-3 β [294].

If FKBP51 could be blocked on a long-term basis, this might result in a pro-carcinogenic effect, as GSK-3 β would be blocked, if to a lesser degree. We presume that potential anti-FKBP51 therapy approaches in diabetes and/or psychiatry would need to be evaluated carefully in terms of potential effects on the signaling pathways in carcinogenesis. Trying to correct the disruption of homeostasis on one side could well result in adverse signaling effects elsewhere.

Anti-fibrotic strategies

Helpful protocols to extract and assay LOX enzymes from tissue samples, cell culture cell layers, and media in the multifunctional LOX family have recently been published [295]. LOXL2 crosslinks collagen by mediating oxidative deamination of lysine residues [296, 297]. LOXL2 promotes dedifferentiation in PyMT tumor-derived cells together with reduced or delocalized E-cadherin [298]. LOXL2 was associated with increased levels of zinc finger protein SNAI1 (Snail) and various cytokines. Additionally, it was concluded that LOXL2 might be necessary for metastasis and facilitates the formation of PCN or metastatic niche formation by triggering the myeloid progenitor CD11b+/Gr1+ cell population but that this effect was independent “of its potential ability to modify ECM stiffness and collagen organization”. LOXL2 represses the canonical Notch homolog 1 (Notch1) pathway and correlates negatively in premalignant tumors [299].

Fibrosis was shown to be attenuated by “combined inhibition of LOXL2 and TGF- β type I receptor (T β RI) activities by trihydrophenolics” [300]. Blocking LOXL2 in thioacetamide (TAA)-induced fibrosis showed attenuation of both parenchymal and biliary fibrosis as well as reversal of fibrosis [301].

Uterine fibroids are seen as non-cancerous growths [302] with a low risk of 0.96% out of 229,536 adult women having unexpected uterine cancer [303]. An anti-fibrotic approach using atorvastatin which inhibits cell proliferation in a dose and time-dependent manner plus stimulating apoptosis by inducing caspase-3 activation, up-regulating Bcl-2 interacting mediator of cell death (Bim) and down-regulating B-cell lymphoma 2 (Bcl-2) and suppressing phosphorylation of ERK1/2 and c-Jun N-terminal kinase (JNK) was reported [304].



Figure 2. (continued) α SMAD: alpha-smooth muscle actin; miR21: micro RNA-21; p300: protein 300 (p300-CBP coactivator family); SP1: specificity protein 1; AP1: activator protein 1; E2F4/5: cytoplasmic complex of Smad3, retinoblastoma-like protein 1 (P107, RBL1), E2F4/5 and D-prostanoid (DP1); p107: retinoblastoma-like protein 1, RBL1; TGF β : transforming growth factor beta; Pro-MMP-9: pro-matrix metalloproteinase 9; Pro-MMP-1: pro-matrix metalloproteinase 1; Pro-MMP-7: pro matrix metalloproteinase 7; SNAI1: zinc finger protein SNAI1; MMP-1: matrix metalloproteinase 1; MMP-7: matrix metalloproteinase 7; MMP-2: matrix metalloproteinase 2; E-Cadherin: CAM 120/80 or epithelial cadherin, cadherin-1, epithelial cadherin; CXCL1: chemokine (C-X-C motif) ligand 1; Osm: oncostatin-M; PI3K: phosphatidylinositol 3-kinase; FOXO3a: forkhead box protein O3a; p120: catenin delta-1, protein 120; Rho: Ras homolog gene family, member A; Rac1: Ras-related C3 botulinum toxin substrate 1; cdc42: cell division control protein 42 homolog; BIM: Bcl-2 interacting mediator of cell death; PUMA: BH3-only protein; CXCR4: C-X-C motif of chemokine receptor 4; cdk2: cyclin-dependent kinase 2; LOXL3: lysyl oxidase homolog 3; mTORc1: rapamycin complex 1; PAI1: Plasminogen activator inhibitor-1.

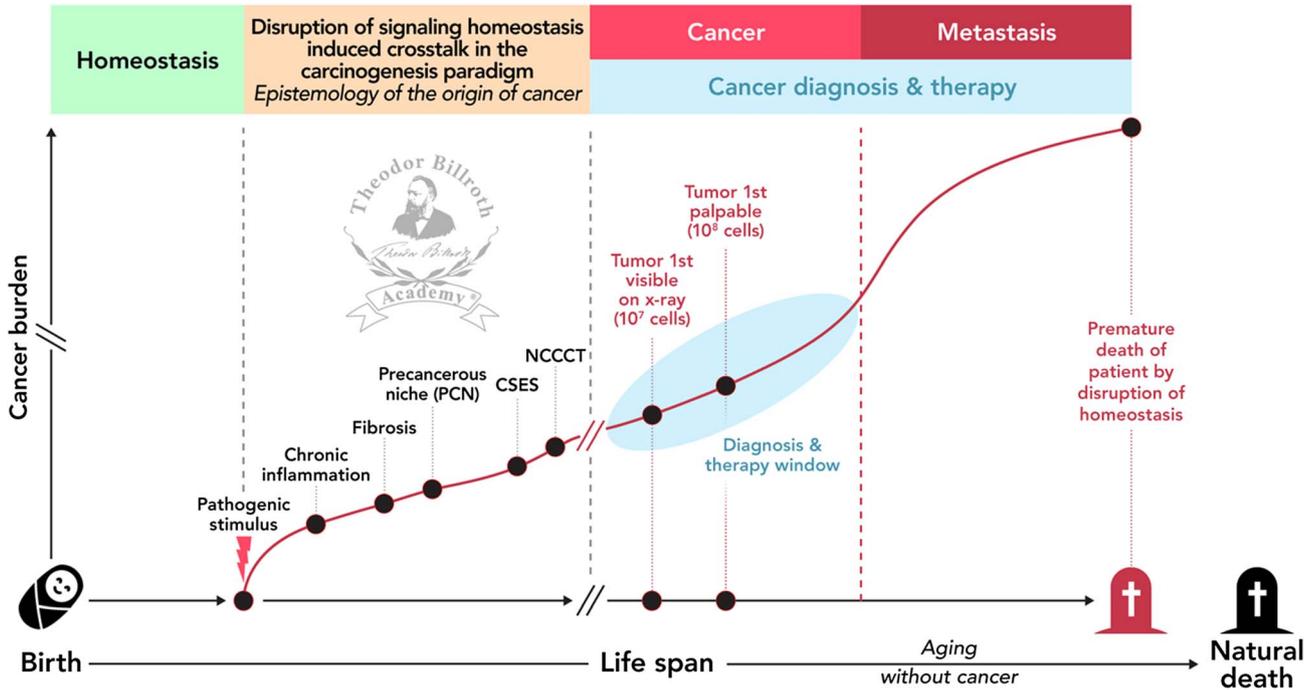


Figure 3. Cancer burden in regard to homeostasis and the disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm “Epistemology of the origin of cancer”. *Explanation numbers:* A tumor nodule is reported to be first detectable by X-ray imaging when it has 10^7 cells [330] which was earlier 10^8 cells [331]. The average number of cells in a tumor when it is first palpable was reported to be 10^9 cells in 2002 [331] which approximately accounts for a tumor with 1g [332]. As it was also reported to be 10^6 cells in 1943 [333], we decided to decrease this number for the illustration by 1 log only to 10^8 cells.

Inhibiting AGTR1 with losartan, in combination with the chemotherapy regime FOLFIRINOX (F-NOX), in locally advanced pancreatic cancer resulted in higher complete macroscopic and microscopic cancer resection rates (R0-resections) [305]. Using losartan in pancreatic ductal adenocarcinoma mice treated with losartan (70 mg/kg) or saline (control vehicle) showed an increase of fractional blood volume and vessel size index plus an increase in the intratumoral uptake of ^{18}F -5FU by 53% in micro-positron emission tomography (PET) [306]. The application of the monoclonal antibody simtuzumab failed to provide evidence of a therapeutic effect in idiopathic pulmonary fibrosis [307]. We consider that this is related to the existence of various alternative splicing isoforms [308] that could explain why a monoclonal antibody to LOXL2 alone might not result into the necessary clinical anti-fibrotic effect.

In this regard it may be relevant that intranasal losartan decreases perivascular beta amyloid, chronic inflammation, and the decline of neurogenesis in hypertensive rats [309]. Even in AD, and other chronic diseases the sequences of pathogenic stimulus followed by unresolved chronic inflammation and fibrosis are important.

The stroma of human pancreatic tumors expresses the vitamin D receptor (VDR) and treatment with a vitamin D3 derivative “the VDR ligand calcipotriol markedly reduced markers of inflammation and fibrosis in pancreatitis and human tumor stroma” with an improvement in gemcitabine responsiveness [310]. To our knowledge, there are

no ongoing and/or planned cancer trials combining anti-fibrotic agents together with calcipotriol and/or anti-inflammatory agents.

Although our current understanding is limited, it would be of interest to know how the quantity of cross-links occurs, as well the “cross-links-types” and how these influence the stroma and the subsequent fate of tumor [300, 311, 312].

In vivo studies in two complementary genetic mouse models with mammary gland specific deletion or overexpression of LOXL2 in the *PyMT* breast cancer model have yielded promising results. The *PyMT* model mimics many processes found in human breast cancer progression generating highly aggressive tumors that metastasize to the lung within 3–4 months [313]. LOXL2 deletion in primary tumors resulted in a dramatic decrease of lung metastases while its overexpression produced increased lung metastases [298].

Cautiously optimistic

We may have overestimated the importance of signaling in experiments in so far as static measurements cannot reveal what occurs over long periods. “Recognition of risk markers that reliably predict disease” is considered important for early cancer screening [314] but methodological approaches need to be taken into account: different signaling markers have different levels to be measured at different

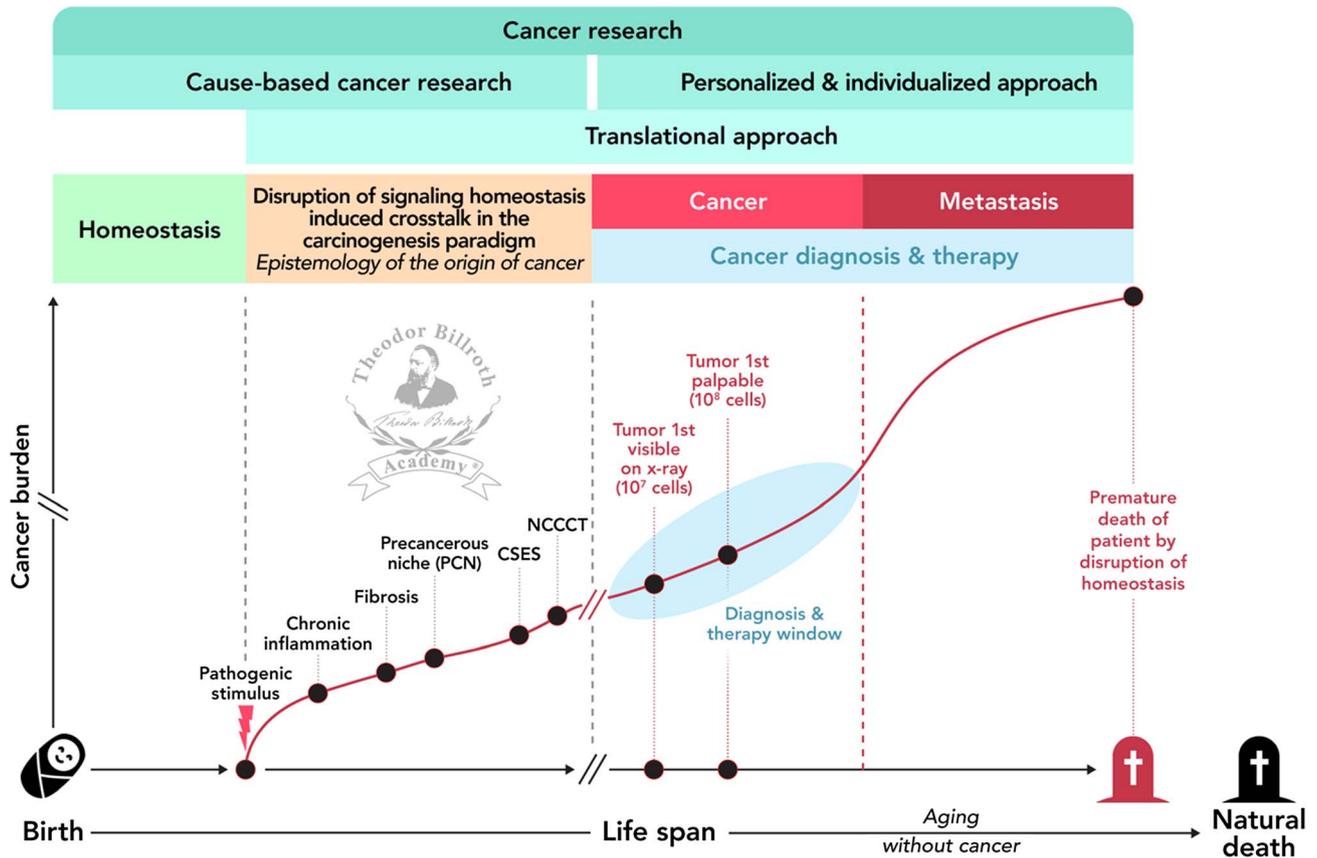


Figure 4. Cancer research strategies and cancer burden within the Disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm “Epistemology of the origin of cancer”. *Explanation numbers:* A tumor nodule is reported to be first detectable by X-ray imaging when it has 10^7 cells [330] which was earlier 10^8 cells [331]. The average number of cells in a tumor when it is first palpable was reported to be 10^9 cells in 2002 [331] which approximately accounts for a tumor with 1g [332]. As it was also reported to be 10^6 cells in 1943 [333], we decided to decrease this number for the illustration by 1 log only to 10^8 cells.

locales within the tumor microenvironment, as for example CK18 at 2 cm sites was higher than at the 5 cm site [315]. In addition, disease itself may induce secondary changes in the expressions of potential biomarkers as was shown in hypertension-induced elevation of connexin 45 (Cx45), and which may affect communication between vascular smooth muscle cells (VSMCs) [316]. The disruption of homeostasis reveals itself through many different facets.

Investigating solid materials at around -243 °C using an ultrasound laser pulse revealed that atoms re-arrange themselves within 350 billionths of a second [317]. Furthermore, an as yet unrecognized helix dissociation pathway which occurred within milliseconds was recently reported [318]. mRNA imaging needs to consider the following: 80% of RNAs have a median half-life of “around 2 min” and some 20% for between 5 and 20 min [319]. RNA collected over the last few decades did not discriminate between RNA separated and collected within 2 min versus between 5 and 20 min or even longer. Quality surrogate variable analysis (qSVA) in RNA-seq as a framework for removing confounding by RNA quality and replication resulted in a three-fold (300%) improvement in replication compared with previous approaches [320].

Summary (Figs. 3–5)

This Special Issue “*Disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm ‘Epistemology of the origin of cancer’*” [111, 113, 144–150] provides evidence that the six-step sequence [5, 6] of events explains carcinogenesis for some 80% of all cancers. These sequences include (1) a pathogenic stimulus followed by (2) chronic inflammation, from which develops (3) fibrosis with associated remodeling in the cellular microenvironment. From these changes a (4) pre-cancerous niche develops, which triggers the deployment of (5) a chronic stress escape strategy, and when this fails to resolve, and (6) the transition of a normal cell to a cancer cell occurs. These six steps, and the detailed analysis provided in this Special Issue, show that cancer originates, at its essence, from a disruption of homeostasis, the biological phenomenon that maintains cellular function within a given range that defines health.

Although underpinned by many observations including a recent case-control study showing that exposure to bovine leukemia virus is linked to human breast cancer [321], the complexity of signaling and crosstalk is vast as re-activation

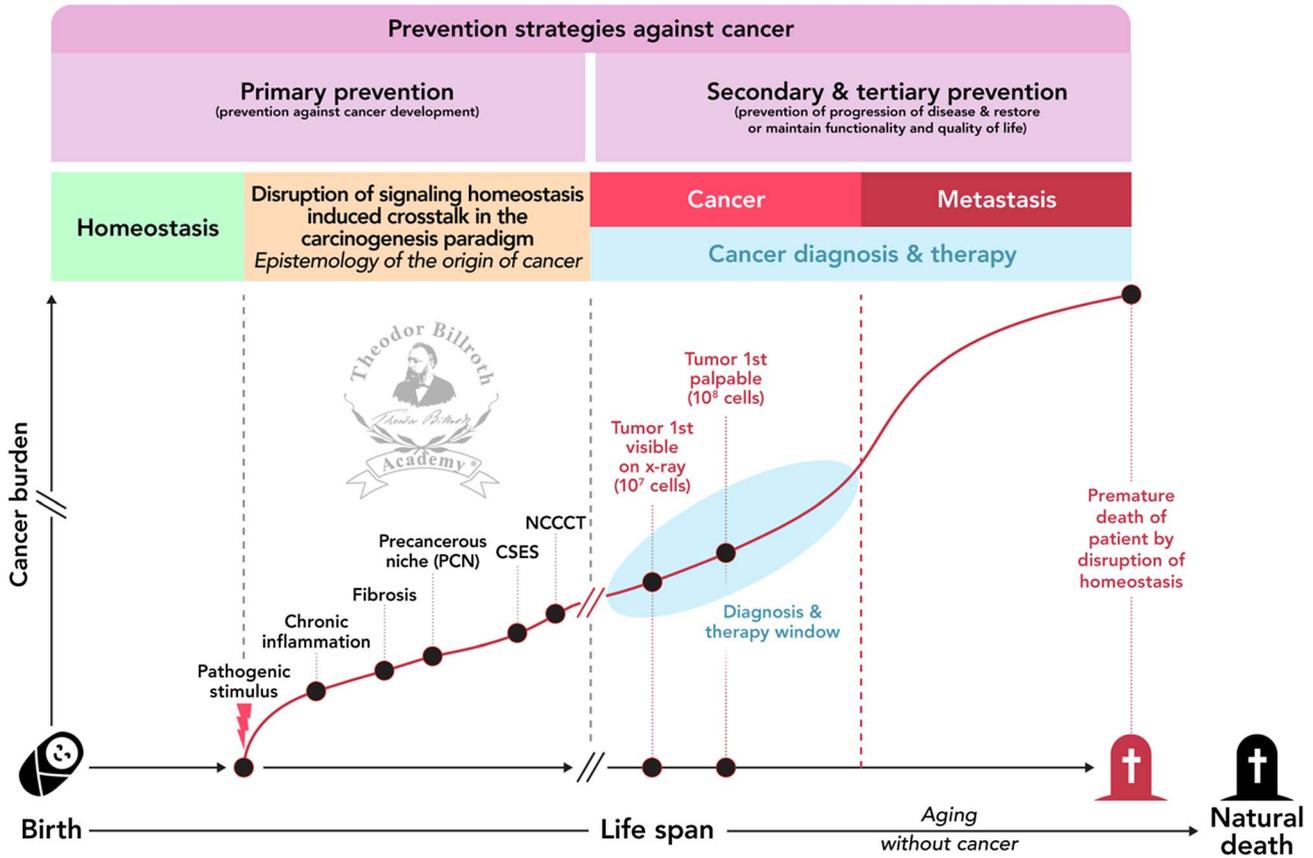


Figure 5. Prevention strategies and cancer burden in regard to homeostasis and the disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm “Epistemology of the origin of cancer”. *Explanation numbers:* A tumor nodule is reported to be first detectable by X-ray imaging when it has 10^7 cells [330] which was earlier 10^8 cells [331]. The average number of cells in a tumor when it is first palpable was reported to be 10^9 cells in 2002 [331] which approximately accounts for a tumor with 1g [332]. As it was also reported to be 10^6 cells in 1943 [333], we decided to decrease this number for the illustration by 1 log only to 10^8 cells.

of latent subclinical inflammation can occur [322]. This may also explain why radiotherapy, after complete tumor resection, can trigger a future PCN and subsequent cancer.

The significance of these findings is evidenced from data that show that retroviruses can create endogenous forms on infiltration into the germline cells of their hosts as the ancestor leukemia delta retrovirus group found in bats are between 20 and 45 million years old [323]. There is little doubt that our understanding of signaling pathways in nature and biology is incomplete. However, this may be viewed in light of the fact that some 99.9% of all somatic mutations that occur within the coding regions of the genome are not fully understood [8, 9].

Furthermore, despite anti-vaccine options eliminating the primary pathogenic stimulus, it is now better appreciated that “curing” cancer by one therapy will not occur in the near future and that multi-step anti-cancer treatments will be necessary. This is underpinned by the knowledge and evidence in regard to therapies, such as reversion of *Helicobacter pylori* (*H. pylori*) induced chronic gastric inflammation and metaplasia which can be accomplished by eradication as a 10-year-follow-up study showed [324, 325].

Additionally, vaccines and anti-fibrotic options have been extensively reviewed. However, to focus on fibrosis alone is not enough. For some 100 years, we have known that there is an inverse ratio of the rate of growth of connective tissue to animal age and a larger amount of connective tissue is produced in young animals and humans which were reproducible for cultured fibroblasts [326–328]. This knowledge needs to be considered in any anti-fibrosis therapy.

Although future studies to investigate the associations of ultra-processed food intake with its influence on the microbiome, morbid obesity, and cancer incidences are warranted, a recent study from the French NutriNet-Santé cohort between 2009 and 2017 investigating 104,980 participants, reported “a 10% increase in the proportion of ultra-processed foods in the diet was associated with a statistically significant increase of greater than 10% in risks of overall and breast cancer” [329].

Despite the need to be cautious in evaluating these findings, they together with the extensive discussions published here [111, 113, 144–150], provide evidence that a much more nuanced view on carcinogenesis is needed. The six-step sequence is much more plausible than a mono-causal carcinogenesis paradigm. The assumptions that genetic

alterations (somatic mutation theory, aneuploidy theory) or cellular metabolism with a consequent energy switch (Warburg theory) alone might explain the etiology of the majority of cancers is not enough to explain cancer as a disease.

Thus, we should not postulate that the majority of cancers originate in genetics and certainly not causally by somatic mutations [9, 113]. It has been previously pointed out that “*Imaging A World Without Cancer is clearly a vision*” and that “*For its realization, a global personalized and individualized anticancer strategy could be fundamental as both could integrate patient- and tumor-associated achievements in research in an adoptable and cost-sensitive manner*” [7]. As mentioned earlier “*In order to meet the challenges in getting there, any newly proposed anticancer strategy must integrate a personalized treatment outcome approach*” [7].

Figure 3 summarizes the cancer burden in regard to homeostasis and the disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm “Epistemology of the origin of cancer”; here a tumor nodule is reported to be first detectable by X-ray imaging when it has 10^7 cells [330] which was earlier reported to be 10^8 cells [331]. The average number of cells in a tumor when it is first palpable was reported to be 10^9 cells in 2002 [331] which approximately accounts for a tumor with 1g [332]. As it was also reported to be 10^6 cells in 1943 [333], we decided to decrease this number for the actual illustration by 1 log only to 10^8 cells.

By extension, we suggest to differentiate cancer research into cause-based, personalized and individualized approaches as well as in translational approaches (Fig. 4). This would include differentiating primary prevention against cancer development versus secondary and tertiary preventive strategies to prevent progression of the disease and to restore or maintain functionality and quality of life (Fig. 5).

As reported recently “*Although science belongs to no one – and to everyone, property (science) obliges*” and “*Our responsibility as scientists is to insure that the generations that follow us cannot write, **Science and research, especially within biotechnology and molecular biology, promised so much and delivered so little***” [334]. This knowledge provides various opportunities for science and research as well as for primary preventive interventions on the onset of cancer as a disease and, to mitigate metastases.

With respect to the provided complex pre-clinical in vitro and in vivo clinical and epidemiological evidence provided within this Special Issue, the six-sequence carcinogenesis paradigm cannot be denied. Our long cognition journey was driven to understand this complicated interwoven multi-step process to describe how a cancer cell develops. Truly, this is a huge challenge to connect and overview the various signaling crosstalk on different levels and without question, many questions remain to be answered with additional experiments and new findings elaborated. We are hopeful that our thinking and scientific work stimulates further thinking in cancer and ultimately

leads to benefits for those who deserve it the most: cancer patients and their relatives.

Nomenclature of abbreviations

5-HETE	5-Hydroxyeicosatetraenoic acid
12-HETE	(5E,8Z,10Z,14Z)-12-hydroxyicoso-5,8,10,14-tetraenoic acid
12(S)-HETE	12(stereoisomer)-hydroxyeicosatetraenoic acid
12(R)-HETE	12(“R” stereoisomer)-hydroxyeicosatetraenoic acid
15-HETE	15-Hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,13E)-15-hydroxyicoso-5,8,11,13-tetraenoic acid
¹⁸ F-5FU	18Fluor-labelled 5-fluorouracil
AA	Arachidonic acid
AD	Alzheimer’s disease
AGTR1	Angiotensin II receptor type 1, AT ₁ -receptor
Akt	Protein kinase B (PKB)
pAkt	Phosphorylated protein kinase B
ALA	α -Linolenic acid, (9Z,12Z,15Z)-octadeca-9,12,15-trienoic acid
ALDH1A1	Aldehyde dehydrogenase 1 family member A1
AMP	Adenosine 3’,5’-monophosphate
AMPK	AMP-activated protein kinase
ANGII	Angiotensin II
AP-2	Activating protein 2
APC	Adenomatous polyposis coli
AS160	Akt substrate of 160 kDa
ATM	ATM serine/threonine protein kinase
Bcl-2	B-cell lymphoma 2
BDPA	Osbond acid, (All-Z)-4,7,10,13,16-docosapentaenoic acid
Bim	Bcl-2 interacting mediator of cell death
BPH	Benign prostatic hyperplasia
BRCA	Breast cancer type protein
CCL2	Chemokine (C-C motif) ligand 2
CD44	Cluster of differentiation 44
CHK2	Checkpoint kinase 2
Co-IP	Co-immunoprecipitation
CRE	cAMP response element
CREB	cAMP response element (CRE)-binding protein 1
c-Rel	Proto-oncogene c-Rel
Cas9	CRISPR-associated protein 9
CDK5	Cyclin-dependent kinase 5, cell division protein kinase 5
CRISPR	Clustered regularly interspaced short palindromic repeats
CyP40	Cyclophilin 40
Cx45	Connexin 45
DesA	Bacterial desaturase
DGLA	Dihomo gamma-linolenic acid

DHA	Docosahexaenoic acid, (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid	LTA4	Leukotriene A4, 4-[(2S,3S)-3-[(1E,3E,5Z,8Z)-tetradeca-1,3,5,8-tetraenyl]oxiran-2-yl]butanoic acid
DNA	Deoxyribonucleic acid	LTB4	Leukotriene B4, (5S,6Z,8E,10E,12R,14Z)-5,12-dihydroxyicosa-6,8,10,14-tetraenoic acid
DPA	Docosapentaenoic acid, 7,10,13,16,19-docosapentaenoic acid	LTC4	Leukotriene C4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-[[[(4S)-4-amino-4-carboxybutanoyl]amino]-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid;
DTA	Docosatetraenoic acid, (7Z,10Z,13Z,16Z)-7,10,13,16-docosatetraenoic acid	LTD4	Leukotriene D4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid;
DXM	Dextromethorphan	LTE4	Leukotriene E4, (5S,6R,7E,9E,11Z,14Z)-6-[(2R)-2-amino-2-carboxyethyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid
E-Cadherin	Epithelial cadherin 1, CAM 120/80	LXs	Lipoxins
ECM	Extracellular matrix	LXA4	Lipoxin A4, 5S,6R,15S-trihydroxy-7E,9E,11Z,13E-icosatetraenoic acid
EGFR	Epidermal growth factor receptor	LXB4	Lipoxin B4, 5S,14R,15S-trihydroxy-6E,8Z,10E,12E-icosatetraenoic acid
EMT	Epithelial to mesenchymal transition	MaR1	Maresin 1, (4Z,7R,8E,10E,12Z,14S,16Z,19Z)-7,14-dihydroxydocosa-4,8,10,12,16,19-hexaenoic acid
EPA	Eicosapentaenoic acid, (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentenoic acid	MaR2	Maresin 2, 13R,14S-diHDHA
ERK	Extracellular signal-regulated kinase	MCS	Multicellular spheroids
ESCC	Esophageal squamous cell carcinoma	MIBP	Muscle integrin binding protein
ETA	Eicosatetraenoic acid, all-cis-8,11,14,17-eicosatetraenoic acid	MMP-2	Matrix metalloproteinase-2, gelatinase A
FA	Fatty acids	MMP-9	Matrix metalloproteinase-9, gelatinase B
FADS2	Fatty acid desaturase 2	MRI	Magnetic resonance imaging
FAK	Focal adhesion kinase	mTOR	Mechanistic target of rapamycin
FK506	Tacrolimus	mTORC1	Mammalian target of rapamycin complex 1
FKBP51	Tacrolimus (FK506) binding protein 5	MUFA	Mono-unsaturated fatty acids
FKBP52	Tacrolimus (FK506) binding protein 4	Nanog	Homeobox protein
GLUT-4	Glucose transporter type 4	NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
GSK-3 β	Glycogen synthase kinase 3 β	NMDA	N-methyl-D-aspartate receptor
Hsp90	Heat shock protein 90	NF-Y	Nuclear factor Y
GAGA	GAGA sequence	NPD1	Neuroprotectin D1, protectin D1, (4Z,7Z,10R,11E,13E,15Z,17S,19Z)-10,17-dihydroxydocosa-4,7,11,13,15,19-hexaenoic acid
GATA	GATA sequence	Oct-4	Octamer-binding transcription factor 4
GFP+	Green fluorescent protein-labeled	p14ARF	Alternate reading frame tumor suppressor protein
HBV	Hepatitis B virus	p16	Cyclin-dependent kinase inhibitor 2A, multiple tumor suppressor 1, p16INK4A
HCC	Hepatocellular carcinoma	p16INK4A	Cyclin-dependent kinase inhibitor 2A, multiple tumor suppressor 1, p16
HCV	Hepatitis C virus	p53	Tumor protein 53
high-LET	High linear energy transfer	p120	Catenin delta-1 is
hMLH1	Human mutL homolog 1, colon cancer, nonpolyposis type 2	PAX	Paired-box genes
HPP1	Hyperplastic polyposis 1	PAX6	Paired-box-gene 6, aniridia type II protein, AN2, oculorhombin
IKK1	Inhibitor of nuclear factor kappa-B kinase 1, inhibitor of nuclear factor kappa-B kinase subunit alpha, IKK- α		
IKK2	Inhibitor of nuclear factor kappa-B kinase 2, inhibitor of nuclear factor kappa-B kinase subunit beta, IKK- β		
IL-6	Interleukin 6		
IL-1 β	Interleukin 1 beta		
JNK	c-Jun N-terminal kinase		
LA	Linoleic acid, cis, cis-9,12-octadecadienoic acid		
low-LET	Low linear energy transfer		
LOX	Lysyl oxidase		
LOXL1	Lysyl oxidase-like protein 1		
LOXL2	Lysyl oxidase-like protein 2		
LOXL3	Lysyl oxidase-like protein 3		
LOXL4	Lysyl oxidase-like protein 4		

PCN	Pre-cancerous niche
PD	Paired domain
PET	Positron emission tomography
PGG2	Prostaglandin G2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroperoxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid
PGH2	Prostaglandin H2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid
PI3K	Phosphoinositide 3-kinase
PP2	Protein phosphatase 2, PP2A
PP2A	Protein phosphatase 2, PP2
PP5	Protein phosphatase 5
pPI3K	Phosphorylated phosphoinositide 3-kinase
PPAR α	Peroxisome proliferator-activated receptor-alpha
qSVA	Quality surrogate variable analysis
RFX1	Regulatory factor X1
RVs	Resolvins
RvD1	Resolvin D1, (4Z,7S,8R,9E,11E,13Z,15E,17S,19Z)-7,8,17-trihydroxydocosa-4,9,11,13,15,19-hexaenoic acid
RvD3	Resolvin D3, (4S,5E,7E,9E,13Z,15E,17R,19Z)-4,11,17-trihydroxydocosa-5,7,9,13,15,19-hexaenoic acid
RvD4	Resolvin D4, (4S,6E,8E,10E,13E,15Z,17S,19Z)-4,5,17-trihydroxydocosa-6,8,10,13,15,19-hexaenoic acid
RvD5	Resolvin D5, (5Z,7S,8E,10Z,13Z,15E,17S,19Z)-7,17-dihydroxydocosa-5,8,10,13,15,19-hexaenoic acid
RvD6	Resolvin D6, (4S,5E,7Z,10Z,13Z,15E,17S,19Z)-4,17-dihydroxydocosa-5,7,10,13,15,19-hexaenoic acid
SB-AC	Small bowel adenocarcinoma
SCD1	stearoyl-CoA desaturase-1, Δ -9 desaturase (D9D)
Snail	Zinc finger protein SNAI1
Sox-2	Sex determining region Y (SRY)-box 2
SPARC	Secreted protein acidic and rich in cysteine
SPMs	Specialized pro-resolving lipid mediators
SREBP-1	Sterol regulatory element-binding protein 1
SRF	Serum response factor
SRY	Sex determining region Y
STAT3	Signal transducer and activator of transcription 3
STAT6	Signal transducer and activator of transcription 6
T3	Triiodothyronine
T β RI	Transforming growth factor beta type I receptor
TAA	Thioacetamide
TAZ	Transcriptional coactivator of YAP with PDZ-binding motif
TCA	Tricarboxylic acid
TGF- β 1	Transforming growth factor beta 1

TGs	Triglycerides
SMT	Somatic mutation theory
VDR	Vitamin D receptor
VSMC	Vascular smooth muscle cell
ω -3-PUFA	n-3 polyunsaturated fatty acid, ω -3
ω -6-PUFA	n-6 Polyunsaturated fatty acid, ω -6
WES	Whole exome sequencing
XP	XERODERMA pigmentosum

Acknowledgments

The manuscripts of this Special Issue were supported by the Theodor-Billroth-Academy[®] (TBA[®]) and INCORE, (International Consortium of Research Excellence) of the (TBA[®]). We express our gratitude to the discussions on the web group of the Theodor-Billroth-Academy[®] (TBA[®]) on LinkedIn, the exchange with scientists at Researchgate.com, as well as personal exchanges with distinguished colleagues who stimulated our thinking all named individually earlier in publications – we thank each one. We want to express our thanks to the excellent peer-reviews we received by the reviewers and the guest editor.

Conflict of interest

The author reports the following conflict of interest: Björn LDM Brücher is Editor-in-Chief in Life Sciences-Medicine of *4open* by EDP Sciences. Ijaz S. Jamall is Senior Editorial Board member in Life Sciences-Medicine of *4open* by EDP Sciences. The authors, of their own initiative, suggested to the Managing Editorial to perform a transparent peer-review of their submittals. Neither author took any action to influence the standard submission and peer-review process, and report no conflict of interest. The authors alone are responsible for the content and writing of the manuscript of this Special Issue. This manuscript contains original material that has not previously been published. Both authors contributed to the discussion on its contents and approved the manuscript.

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Cite this article as: Brücher BLDM & Jamall IS 2019. Synopsis: Special Issue on “Disruption of signaling homeostasis induced crosstalk in 8 the carcinogenesis paradigm *Epistemology of the origin of cancer*”. 4open, **2**, 28.