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REVIEW ARTICLE OPEN ACCESS

Transition from normal to cancerous cell by precancerous niche (PCN) induced chronic cell-matrix stress

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Abstract – The attempt to restore homeostasis, once disrupted, such that complex signaling, crosstalk between ubiquitous proteins, and a diverse range of pathways gone awry is near impossible, especially in the presence of an ongoing pathogenic stimuli with incessant inflammation. This persistent inflammation, when unresolved, induces fibrosis with consequent remodeling of the extracellular matrix (ECM) which leads to the formation of the precancerous niche (PCN), the tipping point in the transition of normal to cancerous cells. Thus, the sustained disruption of homeostasis when confronted with limited adaptation capabilities either of cells or of the surrounding matrix and faced with chronic stress in the tissue microenvironment results in an escape strategy which, if unsuccessful, causes cells, tissue, or the organism to become unable to recover over the long term. All conditions necessary for cell–cell transition such as deregulation of cell–cell complexes, decrease in the stability of adherens junctions, together with the apical-basal polarity, and the loss of the cytoskeletal architecture occurs as a cascade of events inducing inappropriate and diverse signaling pathways and crosstalk. 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. The constant stress that can result in the development of the PCN leads to a chronic stress escape strategy (CSES) which, if unsuccessful, eventually triggers a normal cell- to-cancer cell- transition (NCCCT).

Keywords: β-catenin, AHR, Akt, AP-1, Bcl-2, Cancer, Carcinogenesis, Cell transition, Chronic inflammation, CD44, Cx32, E1Q, E12/E47, EBV, ECM, Extracellular matrix, Epidemiology, Epigenetics, ERK, FADD, Fibrosis, FoxC1, Genomics, GSC, HATs, HGF, LINE-1, microRNA, MMPs, MMP-2, MMP-9, Mutation, NF-κB, OSCC, p107, p130, p300, Pathogenesis, PBX, PI3K, PPAR-γ, Precancerous niche, Proteomics, RB1, RB1CC1, RBL1, SIP1, SP1, Slug, Snail, Somatic mutation theory, SOX, Src, Syk, STAT3, TALE, TCF3, TGF-β1, TIMP-1, TNFR1, TRADD, Twist1, VEGF, ZEB1, ZEB2

Introduction

Cell transition is one of the miracles of biology and occurs by a variety of influences: polarity coordination [1–12], microtubule dynamics [13], various signaling pathway feedback [14] and by factors such as twist-related protein 1 (Twist1), Zinc finger protein SNAI1 (Snail)/zinc finger protein SNAI2 (slug), zinc finger E-box-binding homeobox 1 (ZEB1)/zinc finger E-box-binding homeobox 2 (ZEB2), transcription factor 3 (TCF_3, E2A immunoglobulin enhancer-binding factors E12/E47), homeobox protein goosecoid (GSC), and survival of motor neuron protein-interacting protein 1 (SIP1) [15–19]. For example, deletion of Snail or Twist in a genetically engineered mouse model to suppress the epithelial-mesenchymal transition (EMT) showed that Snail2 (Slug) expression was restricted to early pancreatic intraepithelial lesion without affecting the extracellular matrix (ECM) and fibroblast content, tumor vessel density, intratumoral hypoxia, CD3+ T-cell infiltration, and cancer cell apoptosis, and was associated with induction of chemoresistance to gemcitabine [20].

However, cells can switch between different types of polarity and cell transition needs much more to go awry such as "*signaling networks, transcription factors, membrane-trafficking pathways*" [21].

"*The transition from one cell function to another, as well as the transition of one cell type to another seems to be a*

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routine event rather than a rare one" [22]. The cell–cell communication as well as of the ECM influences the polarity, and perhaps most importantly, malignant transformation of mammary epithelial cells by alterations of the ECM including the complex interplay of various signaling pathways such as the metalloproteinases (MMPs) and their inhibitors, the tissue inhibitors of metalloproteinases (TIMPs) ([23] *reviewed in* [24]).

Tissue inhibitor of metalloproteinases-1 (TIMP-1) can induce hepatocyte growth factor (HGF/scatter factor) accompanied by increased metastasis and triggering of its corresponding genes in colorectal cancer metastasis [25]. In this regard, gelatinases are of for cellular homeostasis as well as for metastasis [26]. For example, *Helicobacter pylori* (*H. pylori*) infected gastric mucosa increases interleukin 21 (IL-21) and promotes gelatinases, matrix metalloproteinase 2 (MMP-2), and matrix metalloproteinase 9 (MMP-9) synthesis through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [27]. The disruption in homeostasis by signaling and crosstalk of ubiquitous proteins [28] in the presence of ongoing pathogenic stimuli induces unresolved chronic inflammation which has been reviewed elsewhere in this Special Issue [29, 30].

Cell transition during carcinogenesis is difficult to break down to just a few signaling pathways, receptors, or cell types. Some specific pathways might be differently affected and/or dependent on other influences, e.g., some signaling will occur during embryology (normal physiology) or influenced by ongoing pathogenic stimulus while different changes in homeostasis may provoke different effects. These may be the reasons why cell transition in general is restricted and why it is necessary to understand in all its complexity. Here we provide information on cell transition with regard to embryology, pathogenic stimulus, the role of the retinoblastoma (RB) protein family and apoptosis, chronic inflammation, and the role of the retinoblastoma coiled coil protein 1 (RB1CC1), fibrosis and its remodeling, all working towards the precancerous niche (PCN). In addition, various signaling pathways such as pituitary tumor transforming gene 1 (PTTG1), catenin beta-1 (β-catenin), sex-determining region Y (Sry)-related high-mobility-group Box (SOX), microRNAs, histone acetyltransferase p300 (p300, adenovirus early region 1A (E1A)-associated protein p300), specificity protein 1 (transcription factor) (SP1), activator protein 1 (AP-1), aryl hydrocarbon receptor (AHR), long interspersed nuclear element-1 (LINE1) and chronic cell matrix stress including STE20-like serine/threonine-protein kinase (SLK) signaling provide insights that are helpful to review so as to unmask the process of cell transition during carcinogenesis.

Embryology

Cell transition is absolutely necessary for embryogenesis and morphogenesis but incompletely understood. However, the "*transition from one cell function to another, as well as the transition of one cell type to another seems to be a routine event rather than a rare one*" [22, 31]. For example, some 50 years ago it was shown that free-floating "peritoneal macrophages" replaced destroyed mesothelial cells via transformation of its original macrophage role to that of mesothelial cells [32, 33]. Chronic lung injury, under some circumstances, can result in transition to cancer [34]. An EMT in embryogenesis/morphogenesis acts in a direction opposite to that of a mesenchymal-epithelial transition (MET) [35]. EMT can induce non-cancer stem cells to become cancer stem cells [36, 37].

Mammalian morphogenesis is complex. The enzymes histone deacetylases (HDACs) remove acetyl groups to promote chromatin compaction ([38] *reviewed in* [39]) and contain 11 enzymes grouped into four classes: class I (Hdac1, Hdac2, Hdac3, and Hdac8), IIa (Hdac4, Hdac5, Hdac7, and Hdac9), IIb (Hdac 6 and 10), and IV (Hdac11) ([30] *reviewed in* [40]). HDACs counteract the promoting effect of histone acetylation on gene expression which is to catalyze an acetyl group to certain lysines in the tails of the core histones H2A, H2B, H3, and H4 by histone acetyltransferases (HATs) [39].

HDAC8 is involved in tissue development [39] and in various diseases. HDAC8 is increased in lung fibrosis and anti-HDAC8 therapy decreases type-1 collagen and fibronectin while increasing the anti-fibrotic peroxisome proliferator-activated receptor gamma (PPAR-γ) [41] and is associated with poor survival in neuroblastoma [42]. HDAC8 knockdown decreases cell proliferation in lung, colon, and cervical cancer cell lines [43]. Furthermore, AHR and HDAC8 are enhanced in liver cancer cell lines and tissues, and HDAC8 inhibition upregulates the cyclin D-retinoblastoma protein (RB, RB1) in vitro and in vivo through AHR [44].

Pathogenic stimulus

Normal to metaplastic gastric epithelial cell proliferation is coordinated by hyaluronic acid cluster-of-differentiation (CD) cell surface glycoprotein (CD44) receptor in *H. pylori*- or tamoxifen-induced atrophy of acid-secreting parietal cells (PCs) [45]. Cell damage induces extracellular signal-regulated kinases (ERK, mitogen-activated protein kinase [MAPK]) signaling resulting in an increase in CD44 which then binds to signal transducer and activator of transcription 3 (STAT3) and reduces the proliferation response. CD44 is encoded by one gene on chromosome 11 [46] and consists of a constant part encoded by exon 1–5 and 16–20 which are included in all isoforms; N- and O-glycosylation increases CD44 heterogeneity and CD44 is synonymous with a large transmembranous proteoglycan surface molecule family.

Transforming growth factor β1 (TGF-β1) increases CD44 and down-regulates microRNA-138 contributing to cell transition [47]. Snail expression and partially Twist1 induce in a β-catenin-dependent manner CD44 expression [48]. Epstein-Barr virus (EBV) promotes latent membrane protein 1 (LMP1) introducing CD44 expression on the cell surface associated with lymphoid tumor growth and dissemination [49] and the EBV-CD44 axis is of importance

in oral squamous cell carcinoma (OSCC) and nasopharyngeal carcinoma (NPC) [50], gastric cancer [51, 52] and Burkitt lymphoma [53].

In vitro experiments of EBV associated keratitis show that transforming growth factor beta 1 (TGF-β1) promotes spleen tyrosine kinase (Syk) and proto-oncogene tyrosine-protein kinase (Src) signaling after phosphatidylinositide 3-kinase (PI3K)/protein kinase B (Akt) and ERK activation resulting in cell transition in human corneal epithelial cells (HCECs) [54] which may be seen as an ignition point for cell-to-cell transition.

The association between pre-B-cell leukemia transcription factor homeobox (PBX) with PBX1-4 in human and *H. pylori* is of interest: *H. pylori* increases the transcriptional factor PBX1 followed by downregulation of connexin 32 (Cx32) [55]. Decreased Cx32 is correlated with "*the degree of tumor cell differentiation with unrestricted growth control*" ([56] *reviewed in* [55]).

Three amino acid extension loop proteins (TALE) play a role in cell differentiation and embryogenesis and include the trimeric DNA-binding complexes of PBX, the regulating protein-1-2 of the Homebox gene (Hox) with PBX/Knotted 1 Homeobox 1 (PKNOX1), PKNOX1-2, PBX-regulating protein-1-2 (PREP1-2), the DNA binding cofactors MEINOX (a contraction of MEIS and KNOX) for PBX and Hox with myeloid ecotropic viral integration site1-3 (homebox protein Meis1-3) [57–59]. However, these transcription factors interact independently in addition to being integrated into multiple pathways. For example, Meis1 acts as a purported oncogene, promoting cell proliferation and resistance to apoptosis, and was reported to be highly expressed in ovarian cancer [60].

Amplification of the Meis1 gene was reported in acute myeloid leukemias [61], neuroblastoma ([62] *reviewed in* [59]). Transcriptome analysis suggested that Meis1 was thought to be involved in carcinogenesis of colorectal adenomas [63]. Splice variants of Meis1 containing Meis1a and Meis1b found in human and mice and two new Meis1d transcripts were found with 27 kD weight ($Meis1_{27}$) in cytoplasm of proximal colon epithelial cells and the Meis1 32 kD variant ($Meis1_{32}$) in the nuclei of non-epithelial cells in the stomach and colon; finding various Meis1 variants in different cell types and subcellular compartments [64]. This may explain the contradictory findings that Meis1D, the homeodomain-less splice variant of Meis1, is found to inhibit gastric [65] and clear renal cell carcinogenesis [66], or to be downregulated in colorectal carcinomas, suggesting that Meis1D is a tumor suppressor [64].

The pioneer transcription factor PBX1 cannot promote carcinogenesis by itself. In esophageal cancer tissues, the transcription factors, Forkhead box C1 (FoxC1) and ZEB2, are associated with both poor survival and disease-free survival: FoxC1 transactivates ZEB2, which also suppresses E-Cadherin, through PBX1, which is a member of the three TALE-class homeodomain families [67]. The TALE homeodomain of PBX1 promotes cell transition in animals and plants [68] and in gastric cancer [69, 70].

Furthermore, the transcription factor, PREP1, also posseses tumor suppressor activity and both PREP-1 and Meis1 require PBX1 with the effect being largely dependent on the level of expression. An increase in expression of PREP1 results in inhibition of Meis1-triggered tumor development but other genes such as AP-1 sequences are associated with Meis1-induced cancer. Blasi et al. reviewed the different PREP1 suppressive and Meis1 oncogenic signatures [59]. PREP1, Meis1, and PBX1 single nucleotides can be found in cancers and, the absence of PREP1, induces DNA damage. The fact that TALE gene amplifications are not frequent in that only 5/287 gastric cancer patients showed a deletion with one patient showing a truncating mutation in PREB1 also suggests that Meis1 alterations are also not very common and reported in 14/178 lung squamous cell carcinomas. This may be due to the fact that the majority of mutations occur after the onset of carcinogenesis as previously proposed [22].

It appears that both PREP1 and Meis1 compete in terms of their suppressive and oncogenic effects in carcinogenesis [59]. This might be relevant since different cancer phenotypes might be dependent on the kind and grade of disruption of their homeostasis at different points in the pathways. PREP1 has been associated with induction of cell transition and cancer spread through the TGF-β/SMAD3 pathway in non-small cell lung carcinoma (NSCLC) [71]. As Meis1 was reported to induce G1/2 arrests and non-apoptotic cell death through decreased levels of Survivin and B-cell lymphoma 2 (Bcl-2) [66], its non-oncogene effect might be a matter of concentration which, in turn, argues in favor of the disruption-of-homeostasis concept in carcinogenesis. Meis1 associated cell growth promotion is directly linked to RB1 cell-cycle signaling [72].

Retinoblastoma (RB) protein family

The RB protein family contains the tumor suppressor RB1, the retinoblastoma-like protein 1 (p107, RBL1), and the retinoblastoma-like protein 2 (p130, RBL2) [73]. RB1 can be inactivated by phosphorylation resulting in cell cycle progression. It is important to note that Rb1 has independent cellular functions depending on its being un-phosphorylated, mono-phosphorylated, or hyper-phosphorylated [74–77]. This condition is also independent from Myc amplification [78]. RB1 binds and inactivates the transcription factors E2 promoter-binding–protein-dimerization partner (E2F-DP) dimers and thus prevents cell cycle progression [79]. This explains why the majority of human OSCC do not express RB1 measured by immunohistochemistry, and that those which express RB1 (some 20%) reveal the inactive (phosphorylated) form [80].

EBV infection is inversely correlated with the expression of RB1 in Reed–Sternberg cells in classic Hodgkin lymphoma [81] and RB2/p130 was inversely correlated with vascular endothelial growth factor (VEGF) expression and tumor aggressiveness in cyclin-dependent kinase inhibitor 1B ($p27^{KIP1}$)-negative hepatocellular carcinoma (HCC) patients and both were independent of tumor staging [82]. An inverse correlation of retinoblastoma protein was observed in head and neck squamous cell carcinoma [83].

Otherwise, it should be noted that the retinoblastoma protein 2 (RB2)/p130 immunohistochemistry (IHC) false positive rate can be as high as 22% [84] and that RB1 degradation by the human papillomavirus (HPV) E7 of the HPV type 16 might overcome the cellular response in high-risk HPV [85]. The necessity of zinc which has been reviewed in this Special Issue in various signaling pathways is also of importance as the E7 carboxyl terminus consists of a zinc-binding motif [86]. HPV E7 proteins even stimulate proliferation independently of their ability to interact with RB [87]. HPV E6/7 proteins can induce a decrease of the human suppressor protein 53 (p53) but also interact by p53 independent pathways inducing apoptosis [88].

Apoptosis

The self-induced death of cells called apoptosis involves "*typical morphological features, such as shrinkage of the cell, fragmentation into membrane-bound apoptotic bodies and rapid phagocytosis by neighbouring cells*" and chromatin condensation, membrane blebbing or ultrastructural modification of cytoplasmic organelles along with activation or suppression of specific signaling and crosstalk pathways [89–92]. At first, it was thought that apoptosis occurs spontaneously in cancers and was largely associated with anti-cancer treatment [93] but there is a difference in apoptosis in existing cancer compared to the development of a cancer cell (carcinogenesis) as here it is not just about how the double-strand cleavage of nuclear DNA occurs.

We now recognize the importance of the interruption of signaling pathways and decreased apoptosis, which typically is necessary for maintaining and regulating homeostasis of chronic cell stress matrix cells. Furthermore, decreased apoptosis is important during carcinogenesis [94]. Most important in the apoptotic process are caspases [95] but also caspase-independent pathways [96, 97] and the interplay between various extrinsic receptors, such as the death type 1 TNF receptor (TNFR1), TNF receptor-associated death domain (TRADD), Fas-associated death domain (FADD), as well as cysteine proteases like caspase 8, and intrinsic pro-apoptotic proteins and the homeostasis between pro-apoptotic proteins Bax, Bak, Bad, Bcl-Xs, Bid, Bik, BIM and Hrk, and anti-apoptotic proteins Bcl-2, Bcl-XL, Bcl-W, Bfl-1 and Mcl-1 ([95, 98, 99] *reviewed in* [94]).

Chronic inflammation

The extensive review of chronic inflammation triggered by pathogenic biological and/or chemical stimulus is presented elsewhere in this Special Issue [29]. Chronic pancreatitis with chronic inflammation is a well-known precancerous condition [100, 101] and the important role of TGF-β1 had been discussed [29].

TGF-β1 induces lysyl oxidase (LOX) expression, secretion, and proteolytic processing in normal as well as in mammary epithelial cells and LOX downregulates the E-cadherin suppressive effect [102] while upregulating vimentin [103, 104]. Both the upregulation of vimentin and the downregulation of E-Cadherin were observed at the mRNA level [104].

Chronic inflammation in mice and human colitis causes inactivation of retinoblastoma protein by hyperphosphorylation with consequent increase of cell proliferation [105]. Furthermore, dietaryinduced obesity in rats results in the downregulation of RB1 [106]. HPV proteins E6 ad E7 bind and inactivate p53 and RB1 [107] and HPV decreases E-cadherin and downregulates RB1, and interestingly, EBV seems to act as a co-factor [108]. The coinfection of *H. pylori* and EBV was reported to increase chronic inflammation being of importance for the severity of gastritis in young patients as well as for the development of gastric carcinogenesis [109, 110].

RB1CC1 is regulator of cell differentiation and proliferation and modulates TGF-β signaling through the RING-type E3 ubiquitin ligase, Arkadia [111].

Retinoblastoma coiled coil protein 1 (RB1CC1)

RB1CC1 is closely related to RB1 expression in various epithelial and mesenchymal cancers [112, 113]. RB1CC1 is correlated with RB1, and RB1CC1 seems to be a RB1 regulator [114]. Furthermore, RB1CC1expression induces pancreatic stellate cells (PSCs) and correlates with pancreatic fibrogenesis [115]. RB1CC1 knockdown decreases alpha smooth muscle actin (α-SMAD), collagen expression and autophagy with consequent inhibition of pancreatic duct ligation-induced pancreatic fibrosis while RB1CC1-triggered autophagy induces PSC activation and pancreatic fibrogenesis in chronic pancreatitis. Comparing human OSCC progression with a mouse model revealed an increase of TGF-β1, N-cadherin, p53 and RB1CC1 with a decrease of E-cadherin from normal oral mucosa to OSCC while it was "*increased in lymph node metastases in both human and mouse samples*" [116]. It was also shown that "*altered ductal carcinoma in situ (DCIS)- associated myoepithelial cells promote the invasive progression of DCIS into invasive ductal carcinoma (IDC) via TGF-β signaling activation*" [117]. Only some 8% of 169 investigated DCIS cases showed an aberrant molecular alteration.

Fibrosis and its remodeling resulting into the precancerous niche (PCN)

The role of remodeled fibrosis in creating the PCN has been reviewed separately in this Special Issue [118]. The decrease of E-Cadherin contemporaneously with ECM degradation appears to be relevant for transition of a normal cell to a cancer cell. The subunit enhancer of the zeste homolog 2 (EZH2) of Polycomb Repressive Complex 2 (PRC2), a complex with histone methyltransferase activity, results in increased expressions of Snail, Slug and vimentin with decreased E-Cadherin expression, and is associated with increased fibrosis together with ECM destruction,

plasminogen activation, downregulating of adherens junctions, and increased cell transition [119]. Inhibiting EZH2 with 3-Deazaneplanocin A (DZNep) results in the inhibition of growth and reduced fibrosis in endometriosis along with an attenuated EMT.

It has been suggested that all LOX family members, but especially lysyl oxidase-like-2 (LOXL2), can facilitate cell transition from normal to cancer as LOXL2 can stabilize Snail and repress E-cadherin, occludin, and estrogen receptor-α, and up-regulate vimentin, fibronectin, and matrix metalloproteinase-14 (MMP-14, MT1-MMP) [103, 104, 120–122]. LOXL2 is thought to induce cell transition via focal adhesion kinase (FAK)/Src signaling [123] in gastric [124], breast [125], and pancreatic cancer [104, 126].

In human breast cancer cells (MDA-MB231), LOXL2 was shown to be inhibited by the flavone 5,6,7-trihydroxyflavone (baicalein) through the primary inhibition of of cysteine-rich protein 61 (CCN1/Cyr61) which weakened the LOXL2-Snail or-Slug interplay and resulted in a subsequent increase of glycogen synthase kinase 3β (GSK-3β)-dependent Snail and Slug degradation, and the decrease of migration and invasion [127]. LOX activates FAK/Src signaling as well as Snail [104, 123, 128] and FAK/Src signaling promotes cell transition [129]. Furthermore, LOXL2 attenuates GSK-3β induced phosphorylation of Snail [120].

LOX phosphorylates p130(Cas) (breast cancer antiestrogen resistance protein 1, BCAR1) resulting in the formation of p130(Cas)/adaptor protein Crk/dedicator of cytokinesis (DOCK180) signaling complex while increasing Rac and cdk42 activity regulating actin filament formation with an increase of the cytoskeleton protein, lamellipodium [123]. Lamellipodium is a myosin-independent mechanosensor [130] that drives cell migration in many normal and pathological conditions [131] and is promoted by Rac [132].

The FAK/p130(Cas)/Rac/lamellipodin complex transduces signaling information from matrix stiffnes into mechanosensitive cell cycling and "*converts external information encoded by ECM stiffness into stable intracellular stiffness and mechanosensitive cell cycling*" and, therefore, has an effect on cell migration as well as on the regulation of the cell cycle [133].

Snail promotes cell transition in a SMAD3/STAT3-dependent manner in chronic pancreatitis associated with diabetes [134]. LOXL2 drives EMT through the inositol-requiring enzyme 1 (IRE1)/X-box binding protein 1 (XBP1) signaling pathway inducing Snail, Slug, ZEB2, TCF_3 which are all direct transcriptional targets of XBP1 [135]. Snail and Slug downregulate E-Cadherin. Loss of E-cadherin expression was associated with cell transition in esophageal spindle cell carcinoma which may trigger Snail neoexpression while N-cadherin appears to be of lesser importance in the pathogenesis of this tumor type [136].

Upregulation of TGF-β driven Wnt inhibitors e.g., Wnt family member 5a (WNT5A), Dickkopf Wnt signaling pathway inhibitor (DKK) 1 and 3, and genes involved in modulation of ECM, including LOX, collagen type V alpha (COL5A1), and thrombospondin 1 (THBS1) showed a more aggressive malignant melanoma phenotype [137]. Interestingly, the antibiotic, salinomycin, inhibits cell transition by downregulation of Wnt/catenin beta-1 (β-catenin) signaling [138].

Bleomycin induces collagen I synthesis in pleural mesothelial cells with increases of vimentin and α-SMAD and decreases in E-Cadherin by TGF-β1/Smad2/3 signaling with associated cell transition [139]. Activating the complex consisting of TGF-β1, lectin-like oxidized low density lipoprotein receptor-1, and krüppel-like factor 6 (KLF6), in lung tissues of diabetic patients results in increased cell transition along with pulmonary fibrosis [140]. A role for *N*-acetyl glucosaminyl transferase during cell transition induced by TGF-β1 signaling was reported [141]. More recently, it has been shown that this occurs via downregulation of non-muscle myosin II-A through c-Jun *N*-terminal kinase (JNK)/P38 mitogen-activated protein kinase (P38)/PI3K pathway in lung cancer [142].

Stiff, but not soft, fibronectin substrates induce cell transition dependent on a contractile phenotype with TGF-β activation [143]. Matrix stiffness promotes Twist1 release from the cytoplasmic binding partner Ras GTPase-activating protein-binding protein 2 (G3BP2) with nuclear Twist1 translocation. Twist1/G3BP2 signaling responds to biomechanical signaling from the microenvironment with invasion and tumor spread and drives cell transition and metastasis [144]. The pro-inflammatory mediator, interleukin 6 (IL-6), enhances Twist1 in fibroblasts and STAT3 phosphorylation with consequent cancer-associated fribroblast transdifferentiation [145, 146]. Furthermore, Twist1 upregulates the nuclear transcriptor protein paired related homeobox 1 (Prrx1) which increases the glycoprotein Tenascin-C (TNC) with consequent positive feedback loop (PFL) by enhancing Twist1 again. The continous Twist1-Prrx1-TNC PFL interaction results in fibrosis in vivo in fibrotic disease and cancer-assosicated stroma and this positive feedback loop can become irreversibly activated [146, 147].

Many other enzymes and proteins are involved in cell transition, such as PTTG1, β-catenin (Catenin beta-1, called armadillo in drosophila), SOX, microRNAs (miRs), p300, SP1, AP-1, AHR, and long interspersed nuclear element-1 (LINE1).

Pituitary tumor transforming gene1 (PTTG1)

The highly aggressive castration-resistant prostate cancers (CRPC) grow outside the prostate into adjacent tissues or metastasize (mCRPC) early with a 5-year survival rate of between 15 and 30% [148, 149]. PTTG1 is upregulated in cancers such as colorectal cancer [150] and CRPC and regulated by IL-6/STAT3 promoting cell transition [151].

In another endocrine tumor, breast cancer, PTTG1 was increased in recurred estrogen receptor positive (ER-positive) breast cancers ([152] *reviewed in* [151]). Ionization radiation can induce senescence in PTTG1-depleted cancer cells [153, 154] and can suppress cancer cell proliferation by induction of cellular senescence; inhibiting autophagy can result in a "*switch from radiation-induced senescence to apoptosis*" [155].

β-catenin

β-catenin (Catenin beta-1, called armadillo in drosophila) was discovered in the 1980s and is a member of the catenin protein family and a subunit of the Ca^{2+} dependent transmembrane cadherin complex ([156, 157] *reviewed in* [158]). It is involved in the β-catenin dependent (canonical Wnt) and -independent (non-canonical Wnt) signaling pathways [159]. β-catenin has tumor characteristics, triggers cancer cell proliferation [160], and is expressed in breast cancer [161], liver [162], colorectal [163], melanoma [164] and leukemia [165].

Dicer, an endoribonuclease, discovered in 2001 [166], is downregulated by β-catenin and reported as a marker for cancer aggressiveness which appears to facilitate the spread of ovarian cancer [167].

The canonical Wnt/β-catenin signaling is co-activated by Smad2 through the histone acetyltransferase activity of p300 [168].

Sry-related high-mobility-group Box (SOX) imbalance (Fig. 1)

SOX factors are regulators of transcription and multiple SOX factors have been reported in mammals in nearly every tissue [169]. The functions of SOX genes, including a phylogenetic study of the SOX family and its role in evolution, have been extensively reviewed [170]. SOX4 is a transcriptional factor expressed in B- and T-lymphocytes involved in embryonic development, but its function in apoptosis and cell fate is not completely understood. SOX4 is necessary during organogenesis of the heart, pancreas, and brain and SOX4 regulates EMT by controlling Ezh2 expression and epigenetic reprogramming [171]. Elevated SOX4 levels were associated with poor outcomes in colon cancer [172], gastric cancer [173], lung cancer [174] and osteosarcoma [175].

miR204 was shown to directly target SOX4 in human renal cancer cells suggesting that it could be a marker for the early detection of metastases [176]. Downregulation of SOX1 was associated with improved survival in HCC suggesting that the imbalance of SOX plays a role in the development of cancer [177].

microRNAs (Fig. 1)

microRNAs (miRNAs) are small non-coding RNA regulating genes in plants, animals and in some viruses and many miRNAs have been observed in association with cancer [178]. miR204 expression was reported as being lower in *H. pylori*- positive gastric mucosal tissue [179]. miR204 directly targets SOX4 and suppress both proliferation and metastasis of gastric cancer AGS cells. miR-204 is not associated with lymph node metastasis or early tumor stages whereas SOX4 was shown to be associated with lymph node metastasis and advanced tumor stages [173, 180]. miR204 is downregulated in severe *H. pylori* associated gastritis as well as *H. pylori*-positive gastric cancer cells, and in a transfection model with hsa-miR-204 mimic/inhibitor oligonucleotides in human gastric cancer cell lines, SGC-7901 and MKN-45, cells suppresses in vitro migration/invasion and proliferation of gastric cancer cells [180]. This may explain why an inverse correlation of miRNA204 with SOX4 was reported viz., higher SOX4 is associated with lower miRNA204 and vice versa and miRNA204 directly targets SOX4.

miR-503 directly targets Cyclin D1 and functions as a tumor suppressor as it reduces Cyclin D1 expression [181] which might be of therapeutic value as high Cyclin D1 levels were associated with decreased survival and higher recurrence rates in esophageal squamous cell carcinoma (ESCC) [182].

miR21 is a regulator of mesenchymal phenotype transition which is triggered by TGF-β [183]. Early fibrosis in chronic obstructive pulmonary disease (COPD) patients shows increased miR21 levels [184]. Increased miR21 levels also result in a decrease of the TGF-β1 regulator Smad7 and this deregulation enhances αSMA-mRNA, protein levels, and collagen accumulation [185].

Programmed cell death protein 4 (Pdcd4) interferes with JNK-mediated phosphorylation of c-Jun and recruitment of the coactivator p300 by c-Jun [186]. miR21 downstream of the tumor suppressor, Pdcd4, results in increased cancer invasion and spread [187, 188]. The disruption of miR21 homeostasis can be seen as miR21 inhibits Smad7 resulting in the withdrawal of the otherwise available negative feedback regulation of TGF-β1 [189] miR21 represses the tumor suppressor phosphatase and tensin homolog (PTEN) [190] and inhibits protein BTG2 (Btg2), protein sprouty homolog 1 (SPRY1), and protein sprouty homolog 1 (SPRY2) that usually negatively regulate the RAS/MAPK/Erk pathway [191] such that in the end the RAS/MAPK/Erk signaling is enhanced. However, the global dysregulation of the microRNA network is more complex than discussed here and much remains to be elucidated in vivo [182, 192].

p300 (Fig. 1)

The enzyme, p300 (synonym: histone acetyltransferase p300, E1A-associated protein p300, EP300), discovered in 1994 [193], is a transcription promoter catalyzing histone acetylation via its histone acetyltransferase activity [194]. p300 and related cyclic adenosine monophosphate (cAMP)-response element-binding-protein was suggested to be "*molecular interpreters" that can parse and/or conjugate the regulatory "words," "phrases," and "sentences" of the genome*" [195]. p300 is involved in TGF-β/Smad mediated alpha 2(I) collagen expression [196] as well as in glomerulonephritis in a pSmad2/3 dependent manner [197].

p300 and had been reported in cancers of the breast [198], lung [199], colon [200], prostate [201] and in leukemia ([202] *reviewed in* [194]). However, its role depends on which cell lines and/or tissue and/or medium is being examined, the method by which p300 is measured, and even if

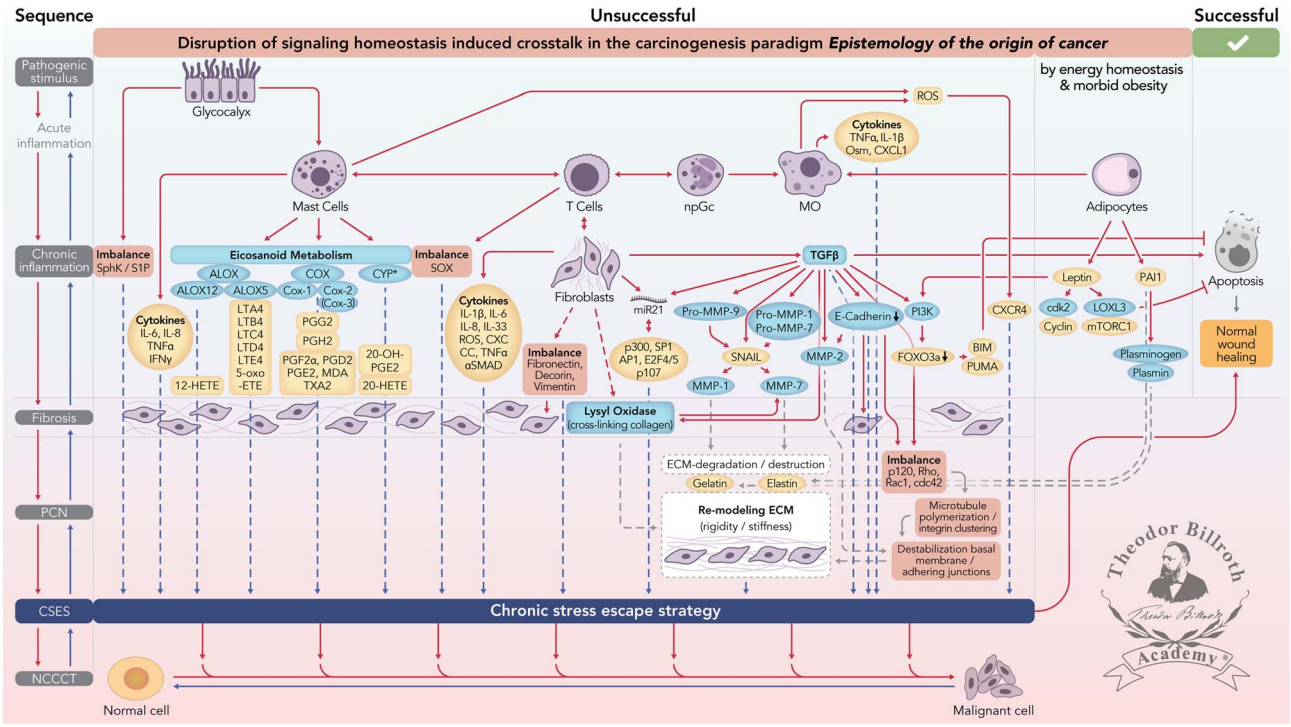

Figure 1. Disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm "*Epistemology of the origin of cancer*". Simplified scheme of the Disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm "*Epistemology of the origin of cancer*" consisting of 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 in paper 3 of this Special Issue [29]. *Nomenclature:* 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): **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; **TNFα:** 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-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 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; **PGFF2α:** prostaglandine 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, 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:** 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-β1:** interleukin beta 1; **IL-33:** interleukin 33; **ROS:** reactive oxygen species; **CXC CC:** chemokine receptors; **αSMAD:** 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; **TGFβ:** 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:** phosphatidylinositide 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.

Wnt/β-catenin activity is involved. Huh et al. found that increased nuclear p300 was associated with improved disease-free survival rates in colorectal cancer patients [203]. As pointed out correctly by Bordonaro and Lazaravo, "*we would expect that cell lines derived from metastases would exhibit a greater degree of CBP-Wnt activity and less p300-Wnt activity compared to matched primary tumor samples from the same patient*" [204].

miR21 downregulates the transformation suppressor Pdcd4 [187], and Pdcd4 usually inhibits the recruitment of the coactivator, p300, by c-Jun [186], suggesting that increased miR21 together with Pdcd4 suppression may be associated with increased p300.

Specificity protein 1 (SP1) (Fig. 1)

SP1 is a member of the SP transcription factor family containing "C2H2-type zinc fingers and resembles the larger family of 'Krüppel-like factors' ([205] *reviewed in* [206]) [Black J Cell Physiol 2001 *reviewed in* Beishline FEBS J 2015] and was first cloned in 1987 [207] [Kadonaga Cell 1987]. Zinc is necessary for nuclear translocation as well as for specific high-affinity binding ([208, 209] *reviewed in* [206]).

SP1 can have dual roles. For example, SP1 binding at the proximal and distal enhancer site activates transcription of the human topoisomerase IIa promoter "*while competition between Sp1 and Sp3 for binding at either the distal enhancer or at both binding regions results in Sp3-dependent repression*" ([210] *reviewed in* [206]).

In cancer, elevated SP1 levels are associated with poor survival and tumor spread in glioma [211], thyroid [212], breast [213], lung [214] and gastrointestinal cancers such as gastric [215] and pancreatic cancer ([216] *reviewed in* [206]).

Fibroblast stimulation results in SP1 phosphorylation and is associated with increased transcription of SP1 [217]. SP1 stability at Ser586 regulates MMP-9 transcription secondary to Erk in alveolar macrophages [218]. Heptatits C virus (HCV)-induced increase of TGF-β1 mediated by p38 MAPK, Src, JNK, and MEK1/2 also induces transcription factors AP-1, Sp1, NF-κB and STAT-3 [219].

Angiotensin-II increases SP1 in a dose- and time-dependent manner; microRNA-7a/b (miR-7a/b) effectively represses TGF-β, ERK, JNK and p38, and inhibits SP1-mediated expression of MMP-2 and MMP-9, and activates fibroblast proliferation [220].

The important interplay between SP1 and chronic inflammation as a sequence in carcinogenesis is supported by the following examples: cytokine-driven PI3K/Akt/Sp1 together with hydrogen sulphide (H_2S) impairs inflammation in an in vitro pancreatitis model [221]. SP1 binds to the promoter of the T-cell-specific T-box transcription factor (TBET) and enhances it in a dose-dependent manner, TBET and interferon gamma (IFγ), in secretion in natural killer (NK) cells and T cells [222]; non-steroidal anti-inflammatory drugs (NSAIDs) inhibited ERK activity with consequent lower SP1 phosphorylation and lower activation of MMP-2 [223].

Blocking the Sp1-TGF-β1/Smad-connective tissue growth factor (CTGF) pathway by miRNA-29b in a rat model inhibited endometrial fibrosis [224]. Decreasing reactive oxygen species (ROS), cyclooxygenase 2 (Cox-2), collagen type II alpha 1 (Col 1A2), calcium, α-SMA, Smad4-p-Smad2/3 co-localization in the cell nucleus, as well as DNA binding activity of SP1, in an early liver fibrosis model was achieved by a maleic acid derivative isolated from the *Antrodia camphorata* mycelium [225]. Knockdown of SP1 resulted in the abolishment of TGF-β1 induced type I collagen production in renal fibrosis by miR-29c downregulation [226].

The Food and Drug Administration (FDA)-approved antihypertensive, Losartan, is an angiotensin II receptor type 1 inhibitor. Losartan (Los) suppresses fibrosis in cardiac muscle in mice [227], as well as inflammation and beta amyloid in rats [228]. Los decreases aszites in ovarian cancer [229], and experimental hepatocarcinogenesis and HCC development together with acyclic retinoid (ACR) [230] as well as tumor progression from DCIS to invasive cancer in breast cancer cell lines [231]. The Los effect appears to be associated through the suppression of THBS1 [232–234] with consecutive decrease of TGF-β1, via decreases in the MAPK and NF-κB pathways in B and T cells [235] and induced antifibrotic miRNAs [229]. Furthermore, Los suppressed "*cell proliferation in a dose-dependent manner, induced apoptosis, decreased YAP (Ser127), and downregulated the YAP target genes CTGF, CYR61, ANKRD1, and MFAP5*" [236]. Los inhibit "*intracellular angiotensin-II production and AGTR2 nuclear localization to enhance the antitumoral effect of 5-FU in an OSCC tumor model*" [237].

The intratumoral distribution and antitumor efficacy of nanoparticles are increased by Los [238]. Los increases paclitaxel efficacy and delivery for ovarian cancer [229], doubled progression free-survival in pancreatic cancer patients [239], reduced cancer-specific mortality in a population-based cohort study gastro-esophageal cancer between 1998 and 2012 from English cancer registries [240], and increased, retrospectively, overall survival by 30 months compared to standard therapy in ovarian cancer patients [229].

Treating pancreatic cancer xenografts with mithramycin (M) and tolfenamic acid (TA) resulted in Sp1 protein degradation and the combined treatment revealed fewer side effects compared to MIT or TA treatment alone [241]. Combining MIT with betulinic acid (BA) in a xenograft mouse pancreatic cancer model resulted in SP1 and VEGF promotion, transcription, and downregulation. This therapeutic regime resulted in fewer side effects compared to gemcitabine [242]. SP1 can function as TGF-β mediated increased expression [243] and it has been reported to play a role in cell transition in gastric carcinoma cells which can be inhibited via miRNA-223 [244]. Dehydroandrographolide is an extract from the herbal medicine, *Andrographis paniculata* (*Burm f*), which upregulates tissue inhibitor of metalloproteinase-2 (TIMP-2) and downregulates NF-κB, SP-1 and AP-1 expression with consequent MMP-2 inhibition suppressing cell transition, cancer cell migration and invasiveness [245].

AP-1 (Fig. 1)

AP-1 is composed of Jun (c-Jun, JunB, JunD) and Fos proteins (c-Fos, FosB, Fra-1, Fra-2) and is involved in inflammation, wound healing, and cancer [246]. Increased Fra-2 was shown to induce remodeling with chronic inflammation and fibrosis questioning the autoimmune cause of idiopathic pulmonary fibrosis (IPF). AP-1 can be induced by platelet-derived growth factor (PDGF) [247] or *Bacteroides fragilis*-induced enteritis together with Ras and MAPK signaling [248]. Furthermore, it can increase matrix metalloproteinase-7 (MMP-7, pump-1 protease, PUMP 1) [249]. AP-1 is also associated in HPV-induced cervical cancer [250] and radioresistance [251]. Increases in interleukin 13 (IL-13) by AP-1 induces TGF-β1, triggering fibrosis in the bleomycin model [252].

Salvia miltiorrhiza extracts, used in traditional Chinese medicine for gynecological diseases, have an anti-inflammatory effect [253] and inhibit AP-1 suppressing 12-O-tetradecanoylphorbol-13-acetate (TPA)-treated MCF-7 cells and MMP-9 expression [254]. Otherwise, AP-1 and mitogen-activated protein kinase (MAPK) was shown to increase MMP-9 expression in fibroblasts [255]. The PI3K and MAPK paths are involved in MMP-9 increase and are also regulated by AP-1, NF-κB or SP1. Blocking ERK/AP-1 and protein kinase C (PKC) extracellular signaling by 3,5,7,3′,4′-pentahydroxylflavone (QUE, Quercetin) suppresses MMP-9 in breast cancer cells [256].

TGF-β1 increases AP-1 through CD44V6/ERK1/early growth response protein 1 (EGR1) signaling [257] and miR-21 expression was shown to be increased in the Jun/AP-1 psoriasis-like mouse model [258]. The miR21 promoter region provides binding sites for AP-1 [259]. miR21 inhibits Pdcd4 and upregulation of miR21 "*is mediated by AP-1 components c-Jun and c-Fos in SP cells*" [260]. AP-1 inhibition by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is dependent from AHR [261].

Aryl hydrocarbon receptor (AHR)

AHR is a cytosolic transcription factor with pro- and anti-inflammatory activity and serves as a central modulating receptor of inflammatory response [262]. AhR was discovered as a specific binding site to TCDD [263], inducing aryl hydrocarbon hydroxylase [264], with proven AHR induction by TCDD [265]. Later, it was proven that cytosolic AHR translocates temperature-dependent into the nucleus which is necessary to induce cytochrome P450 [266, 267] and that aryl hydrocarbon receptor nuclear translocator (ARNT) is an essential dimerization partner for the AHR [268].

AHR is usually inactive and a higher expression is associated with breast cancer [269–272]. AHR is thought to directly increase c-myc mRNA and c-Myc protein [273] which may explain why c-myc expression is also increased in breast cancers [274–278] as well as in various other cancers, such as leukemia, lymphoma, plasmocytoma [279–281], lung cancer [282, 283], neuroblastoma [284], liver cancer [285, 286], testicular cancer [287], or colorectal cancer [288, 289].

Constitutive NF-κB activation is increased in both breast cancer tissues and cell lines [290] and there is a direct association between the NF-κB subunit RelA and AHR in murine hepatoma cells [291]. Kim et al. showed in malignant and non-malignant breast cell lines, that RelA and AHR but not NF-κB RelB or c-Rel subunits build a transcription factor complex resulting in c-myc gene expression [292]. "*The pleiotropic interleukin (IL)-6-type cytokine oncostatin M (OSM) is an inducer of AHR mRNA and protein expression in human HepG2 hepatocarcinoma cells*" [293] and AHR-dependent IL-6 expression which is associated with IL-β1-induced binding of NF-κB components [294]. AHR-inhibition, but not cytochrome P450, family 1, subfamily A, polypeptide 1 (CYP1A1) inhibition, induces transcription factor p65 encoded by RELA gene (RelA), transcription factor encoded by the RELB gene interacting with NF-κB (RelB), nuclear factor kappa-light-chain-enhancer of activated B cells 1 (NF-κB1), nuclear factor kappa-light-chain-enhancer of activated B cells 2 (NF-κB2) and MMP-1 promoting cancer invasiveness. Additionally, there is a different mechanism affecting 12-hydroxyeicosatetraenoic acid (12-HETE). Inhibiting NF-κB2 is associated with induced AHR, CYP1A1 and 12-HETE synthesis and both CYP1A1 and NF-κB can be inhibited in vitro by the alpha-2A adrenergic receptor (α_{2A} receptor) agonist guanfacine and ethyl apovincaminate (vinpocetine) [295].

AHR deletion was associated with "*failure to control Citrobacter rodentium infection due to unrestricted intestinal stem cell (ISC) proliferation and impaired differentiation, culminating in malignant transformation*" [296].

AHR deficiency is enhanced by chronic inflammation in colon carcinogenesis. Otherwise, AHR activation by AHR dietary ligands such as dietary components and tryptophan metabolites regulated intestinal crypt stem cell differentiation and was associated with prevention of carcinogenesis in mice through really interesting new gene (ring) finger protein 43 (Rnf43) and the cell-surface transmembrane E3 ubiquitin ligase zinc and ring finger 3 (Znrf3, homologue of Rnf43), E3 ubiquitin ligases with inhibition of Wnt-β-catenin signaling and consequent decrease of ISC proliferation. This may underpin the integrity role of AHR acting as a host defense [297].

Applying the potent AHR ligand, TCDD, in lymphoma cells (U937) increased "*mRNA levels of cyclooxygenase-2, interleukin 1beta, and tumor necrosis factor-alpha*" in a dose-dependent manner with enhanced MMP-1, matrix metalloproteinase 3 (MMP-3, stromelysin-1), matrix metalloproteinase 12 (MMP-12, macrophage metalloelastase, MME), and matrix metalloproteinase 13 (MMP-13, collagenase 3) and TCDD stimulated macrophage cell migration and promoted its differentiation into atherosclerotic plaque-forming foam cells [298].

Therapy with the AHR agonist TCDD in mice induced fibrosis markers (collagen 1A1 and α-smooth muscle actin), with increased interleukin-1 beta, tumor necrosis factor α and fibroblast activating fibroblast-specific protein 1

(FSP1, S100A4) together with an increase of TGF-β and Snail with an decrease of E-Cadherin and Claudin 1. The fibrosis was histologically apparent after 6 weeks [299]. As AHR knockout rats are insensitive to repeated TCDD exposure, AHR seems to be a regulator of fibrosis and carcinogenesis following TCDD treatment [300]. TCDD treatment at first increased rodent hepatic stem cells (rHpSCs) followed by a loss of loss of viability of hepatoblasts (rHBs) [301]. TCDD promotes cell transition through AHR-mediated EGFR/ERK signaling [302].

A catabolite of tryptophan, kynurenine (Kyn), was shown to be excessively produced by glioma cells through tryptophan-2,3-dioxygenase (TDO) with consequent binding and activation of AHR [303]. AHR was found to downregulate TGF-β signaling in non-neoplastic astrocytes and "*constitutive AHR activity positively controls TGF-β1, TGF-β2 and latent TGF-β-binding protein-1 protein levels in malignant glioma cells*" and AHR inhibition resulted in lower survival and invasiveness of glioma cells [304].

Although indoleamine-2,3-dioxygenase 1 (IDO1) and IDO2 are expressed in human cancers it was shown, that levo- but not dextro-1-methyl tryptophan (D-1MT) inhibits tryptophan catabolism [305]. Otherwise D-1MT reduces tumor CD133+ cells, Wnt/β-catenin and NF-$\kappa\beta$p65 and decreases TGF-β, IDO, chemokine (C–C motif) ligand 5 (CCL5, RANTES), and programmed death-ligand 1 (PD-L1) in murine pancreatic adenocarcinoma [306]. The selective IDO inhibitor and synthetic analog of tryptophan, 1-methyl tryptophan (1MT) increases in vitro the AHR nucleo-translocation and response in mesenchymal stromal cells [307]. AHR is associated with MMP-1 [308], MMP-9 increase [309–311]. The carcinogen, benzo[a]pyrene, triggers MMP-9 together with c-myc expression which is mediated through AHR and ERK signaling [312] and decreasing AHR inhibits gastric cancer cell growth and invasiveness [313].

Heat-shock protein 90 (Hsp90), binds to cytoplasmatic AHR and chaperones with nucleus translocation and dimerization of AHR with ARNT and dissociation of chaperone proteins. The xenobiotic responsive element (XRE, AAH response element, AHRE) [314] binds to AHR with induction of cytochrome isoform (CYP*) [315] such as CYP1A1, CYP1A2, CYP1B1, CYP2S1 and glutathione-S-transferase (GST) and uridine glucuronosyltransferases (UGT) ([316] *reviewed in* [317]). Benzo[a]pyrene (B[a]P) is an inducer of CYP1A1 while AHR is present; topical B[a]P application only induces skin cancer in AHR positive mice [318] using AHR-mediated enzyme induction as an anti-cancer strategy [317, 319].

In terms of the proposed sequences of carcinogenesis [22, 31, 320], dioxin induces leukotriene B4, (5S,6Z,8E,10E, 12R,14Z)-5,12-dihydroxyicosa-6,8,10,14-tetraenoic acid, LTB4) through AHR [321] and AHR mediates fibroblast migration through upregulated arachidonic acid metabolism [322]. Hexachlorobenzene (HCB) induces chronic inflammation increasing MMP-9 via c-Src kinase with disruption of eicosanoid homeostasis by upregulation of Cox-2, prostaglandin E2 (Z)-7-[(1R,2R,3R)-3-hydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid, PGE2) and omega-3 fatty acids eicosapentaenoic acid (EPA) receptor with implication of AHR and induction of endometriosis in vitro [323]. Using rat liver and human-derived hepatoma cell line, HepG2, it was shown that HCB induces an increase of AHR expression, cell proliferation and "*cyclin D1 protein levels and ERK1/2 phosphorylation in a dose-dependent manner*" which is mediated by AHR promoting liver carcinogenesis [324].

Recently AHR was reported to act as a repressor of inflammation associated in colon cancer [325]. These contradictory dictionary findings can be explained as was clearly shown that the concentration on one variable will not be enough to understand complexity and that AHR is involved in carcinogenesis but CYP isoforms will not be expressed in AHR knockdown mice AhR(−/−) mouse and that CYP1A1 is needed [318]. This reveals how just looking at findings in one knockout mouse model without simultaneously taking into account coactivator and/or associated other necessary variables and mediators will result in complete contradictionary findings and interpretations. Moreover, AHR negatively cross-talks with NF-κB but not with CYP1A1 [295]. The AHR ligand 6-formylindolo (3,2-b) carbazole (Ficz) is an AHR agonist in zebrafish inducing various CYP* such as CYP1A1, CYP1B1 [326] which explains why Ficz is protective against AHR-mediated chronic inflammation and downregulates interleukin 7 (IL-7) and dextran sulfate sodium (DSS)-induced colitis in wild-type C57BL/6J mice [327]. We assume that assessing AHR can only be accomplished by taking into account the eicosanoid pathway and its cytochrome P450 pathway, including its many isoforms which has been reviewed in this Special Issue [30].

AHR-mediated carcinogenesis with the disruption of eicosanoid homeostasis as reviewed recently [30], is involved in breast cancer [328, 329], colitis associated colon cancer through miR-132 expression after AHR activation by TCDD [330].

B[a]P induces AHR-dependent IL-10 increase with chronic inflammation [331] and AHR is involved in inflammatory fibrosis of the pancreas [332] and the liver [333]. It depends whether or not AHR is already translocated from its inactive cytoplasmic form to the nucleus.

L-kynurenine ((S)-2-Amino-4-(2-aminophenyl)- 4-oxobutanoic acid) is a metabolite of the amino acid L-tryptophan through tryptophan dioxygenase in the liver and indoleamine 2,3-dioxygenase (IDO) by various human cells; IDO derived Kyn is an endogenous ligand of the human AHR, which is increased in chronic inflammation, promoting cancer cell survival and metastasis in brain cancer cells [303]. The D-enantiomer of kynurenine, D-kynurenine (D-Kyn), is increased in lung cancer cells and is associated with increased vimentin and increases in CYP1A1 and AHR nuclear translocation promoting cell transition [334]. Inactivating the dioxin-like polychlorinated biphenyl (PCB), PCB126, stimulates upregulation of ROS through AHR. Promoting cell transition is in this instance regulated through signal transducer and activator of transcription 3 (STAT3)/Snail1 which is dependent on pyruvate kinase M2 (PKM2) [335]. High expression of its

members IDO, STAT3 and the AHR target gene CYP1B1 is associated with reduced relapse-free survival in lung cancer patients [336]. GSK-3β suppresses ESCC growth via STAT3 [337] but it seems that AHR is involved as well. Inactivating GSK-3β by the aminopyrimidine derivative CHIR-99021 reverses vimentin degradation in AHR overexpressed H1299 cells but it depends where AHR is increased/activated. Cytoplasmatic (inactive) AHR suppresses cell transition via augmentation of mesenchymal vimentin level, and GSK-3β Ser-9 hyper-phosphorylation [338].

The AHR-TGF-β1 crosstalk is also complex. AHR can downregulate TGF-β1 signaling through latent transforming growth factor-beta binding protein 1 (LTBP-1) [339] or result in a deregulation of TGF-β1 secretion [340], but there is an association between AHR, TGF-β1 and the repetitive DNA sequence long interspersed nuclear element-1 (LINE1) which sheds a new light on carcinogenesis and cancer associated findings.

Long interspersed nuclear element-1 (LINE1)

Human transposable elements include RNA and DNA families, and RNA transposons (retrotransposons, retroelements) are divided into long-terminal repeat (LTR) LTR)-containing or non-LTR groups and "*The active, human non-LTR group includes LINE-1 (or L1), next to short interspersed elements (SINE) represented by Alu, and the more recently characterized SVA elements*" and estimated some 45% of the human genome originates from transposable elements [341, 342]. LINE1 "*retrotransposons make up a significant portion of human genomes, with an estimated 500 000 copies per genome*" [343].

LINE-1 is regulated and repressed in human tissue by DNA methylation [344–347] and "*long-term NSAID use and a normal BMI were associated with increased LINE-1 DNA methylation*" as well as a healthy life-style [348, 349]. Chronic inflammation, oxidative stress, and environmental changes can induce and restore LINE-1 methylation [350–353] but not in gingival inflamed tissues [354]. LINE-1 is reactivated by the AHR agonist (B[a]P) through TGF-β1 signaling in human liver cancer samples "*at various stages of malignant progression*" [355].

The association of chronic inflammatory, environmental, oxidative stress and external pathogenic stimuli induced somatic LINE-1 restoration without the need of any mutations together with AHR and CYP* findings should cast a new light in the observed LINE-1 transpositions observed in various diseases and cancers.

LINE-1 demethylation and restoration (*reviewed in* [341, 342, 344]) is associated with neuronal development [356, 357], inflammatory diseases [358], colitis [359], disruption of the adenomatous polyposis coli (APC) gene [360], colorectal cancer [361, 362], breast cancer [363–365] or liver cancer [366].

"*Factors belonging to the family of the testis-determining factor gene SRY (the SOX family)*" regulate LINE-1 [367] and Dicer, which is downregulated by β-catenin and decreased in aggressive cancers [167], and which negatively regulates LINE-1 [368]. A LINE1 transcript "*driven by an HBx promoter, referred to as HBx-LINE-1*" activates Wnt/β-catenin signaling, promotes cell transition, and is expressed in HCC in mice and associated with poor survival and HBx-LINE-1 [369]. LINE1 inhibition results in altered cell morphology [370, 371] and reversed cell transition (*Fig. 2 from* [372] *not shown*).

LINE1 hypermethylation as well as transcription factor SOX-11 (SOX11) and insulin-like growth factor 2 (IGF2), solute carrier family 22 (organic anion/cation transporter), member 12 (SLC16A12), P2X purinoceptor 7 (P2RX7) and myogenic differentiation 1 (MYOD1) were associated with *H. pylori* infection status and atrophic gastritis, which are precancerous conditions of gastric cancer [373]. LINE1 and IGF2 methylation in the leukocyte DNA hypermethylation was associated with more aggressive gastric cancer and progression [374].

Chronic cell matrix stress

Activin A receptor like type (ALK)

p120 selectively inhibits the small GTPase Ras homolog gene family, member A (RhoA) activity both in vitro and in vivo [375]. TGF-β1 induces cell transition via increased RhoA activity [376] which is dependent on activin receptor-like kinase 5 (ALK5) [377].

The transmembrane serine/threonine receptor kinase, activin A receptor like type 1 (ALK1), functions as an alternative type I receptor for TGF-β and increases in ALK1 occur due to elevated MMP-13. The interaction between ALK1 and the TGF-β type I receptor activin-like kinase 5 (TβRI or ALK5) with its ALK1/ALK5 ratio is age-related with a shift to decreased ALK5 in aged mice [378]. ALK1 signaling via MMP-13 results in type II collagen degradation. In young animals, ALK5 is protective of collagen degradation but during aging the ALK1/ALK5 ratio changes as does the role of TGF-β. This maybe relevant as ALK1 is involved in angiogenesis [379] and lends credence to why anti-ALKL1 therapy may be useful in certain cancer therapies [380].

Protein 120 (p120, catenin delta-1)

The shift in localization of protein 120 (p120, catenin delta-1) was associated with a decrease in RhoA activation, and E-cadherin loss which resulted in decreased mobility of cells [381]. In p53-deficient mice, the tumor suppressor p120 "*is dominant over E-cadherin inactivation and its inactivation promotes the development of basal, EMT-type invasive mammary tumors*" [382]. Due to an increase of TGF-β [383, 384] and a decrease in E-Cadherin, the long isoform of p120 dissociates from the membrane and accumulates within the cytoplasm [385]. The p120 family shows redundancy including delta catenin (δ-catenin, cadherin-associated protein 2, CTNND2, neural plakophilin-related arm-repeat protein, NPRAP), armadillo repeat protein deleted in velo-cardio-facial syndrome (ARVCF), armadillo protein p0071 (plakophili4), the more distantly related plakophilins 1–3, which

regulate cadherins important for cell-cell communication and for adhesion [386].

The RhoGTPase family consists of, among others, RhoA, cell division control protein 42 homolog (Cdc42), and Ras-related C3 botulinum toxin substrate 1 (Rac1) [387]. The chemokine growth-regulated purported oncogene 1 (Gro-1) [388] binds to C-X-C motif chemokine receptor 2 (CXCR2, Interleukin 8 receptor, beta, IL8RB) receptors [389], is activated by the small GTP-binding protein RAS, and induces senescence of fibroblasts with consequent stromal reprogramming facilitating carcinogenesis, which is why it is considered a potential target in cancer therapy [390].

Ras is activated by epidermal growth factor (EGF) with consequent RAS movement from an inactive GDP-bound state to an active GTP-bound state [391]. p120 can increase Cdc42 and Rac without altering Rho activity [392]. It is considered that the localization of p120 affects cell motility. p120 activates Rac1/MAPK signaling in breast cancer cells [393] but p120 can also be regulated depending on cancer cell type and through inactivation of E-cadherin [394].

Increased cytoplasmic p120 levels were observed in invasive gastric cancer [395] and loss, or even p120 translocation into the cytoplasm, was associated with cancer and with disease progression [394]. *H. pylori* induced MMP-7 expression is regulated by p120 and Kaiso [396], which is "*a novel member of the rapidly growing BTB/POZ (Broad complex, Tramtrak, Bric à brac/Pox virus and zinc finger) family of zinc finger (ZF) transcription factors (hereafter referred to as POZ-ZF proteins*" [397]. The interaction between p120, Rho and cadherins is complex [398], as Rho increases, Rac activity increases through loss of p120 [399].

ECM remodeling through Rac and Cdc42 activation was shown in rat fibroblasts [400]. Silencing of the Rac1 gene results in increased degradation of the ECM, suggesting that Rac1 inhibitors might play an important role in cancer therapy [401]. Rac1 silencing in lung cancer cells was also associated with inhibition of NF-κB with a corresponding decrease in cell proliferation [402].

The ROS-mediated Src activation also increases tyrosine phosphorylation of p120-catenin with consequent p120 translocation [403]. As mentioned earlier, the p120 translocation and cytoplasmatic accumulation due to continuous TGF-β and LOX activation influence ECM remodeling and "*this process may be seen as the starting point for the chronic-stress escape strategy as proposed*" [22, 31].

Summary

In nature, cells routinely undergo both de-differentiation and re-differentiation. The transition of one cell type to another, including its transition from one cell function to another is incompletely understood mechanistically. Science has learned from embryogenesis and morphogenesis that this biological process is routine and not an exception. The normal cell to cancer cell transition occurs when the necessary groundwork has been prepared by sequences that include pathogenic stimuli, chronic inflammation, remodeled fibrosis (PCN) and a failed chronic stress escape strategy (CSES) that results in a disruption of homeostasis essentially creating an imbalance of pro- and contra- cell transition conditions (Fig. 1). The multiplicity of pathways and signaling events that a cell, tissue, or organism can enlist to prevent or abort the transition from a normal to a cancer cell in a sequenced process that describes carcinogenesis does not need the invocation of somatic mutations. Many of the pathways and signaling mechanisms described involve biochemical processes that are a routine part of a dynamic homeostasis involved in growth and development. Thus, an overview of these complex inter-connected "*Disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm Epistemology of the origin of cancer*" plays a key role in the development of cancer although current understanding does not permit a weight-of-evidence risk assessment on the importance of any given signaling pathway or biochemical mechanism. Despite that limitation, the data strongly support crucial roles for inflammation and fibrosis via a PCN-sequenced event that comprises carcinogenesis.

Nomenclature of abbreviations

1MT	1-methyl tryptophan
5-oxo-ETE	(6E,8Z,11Z,14Z)-5-oxoicosa-6,8,11, 14-tetraenoic acid
12-HETE	12-hydroxyeicosatetraenoic acid
20-HETE	20-hydroxyeicosatetraenoic acid, (5Z,8Z,11Z,14Z)-20-hydroxyicosa-5,8,11,14-tetraenoic acid
20-OH-PGE2	20-hydroxy prostaglandin E2
α_{2A} receptor	Alpha-2A adrenergic receptor
αSMAD	Alpha-smooth muscle actin
β-catenin	Catenin beta-1
δ-catenin	Delta catenin, cadherin-associated protein 2, CTNND2, neural plakophilin-related arm-repeat protein, NPRAP),
ACR	Acyclic retinoid
AHR	Aryl hydrocarbon receptor
Akt	Protein kinase B
ALK	Activin A receptor like type
ALK5	Activin receptor-like kinase 5
ALOX	Lipoxygenase, arachidonate lipoxygenase
ALOX12	12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type
ALOX5	5-lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase
AP-1	Activator protein 1
ARNT	Aryl hydrocarbon receptor nuclear translocator
ARVCF	Armadillo repeat protein deleted in velo-cardio-facial syndrome
B[a]P	Benzo[a]pyrene
BA	Betulinic acid

BCAR1	Breast cancer anti-estrogen resistance protein 1, p130(cas)
Bcl-2	B-cell lymphoma 2
BIM	Bcl-2 interacting mediator of cell death
BTG2	Protein BTG2 (NGF-inducible anti-proliferative protein PC3)
cAMP	Cyclic adenosine monophosphate
CCL5	Chemokine (C-C motif) ligand 5, RANTES
CCN1/Cyr61	Cysteine-rich protein 61
CD44	Hyaluronic acid cluster-of-differentiation (CD) cell surface glycoprotein
Cdc42	Cell division control protein 42 homologue
cdk2	Cyclin-dependent kinase 2
Col 1A2	Collagen type II alpha 1
COL5A1	Collagen type V alpha
COPD	Chronic obstructive pulmonary disease
Cox	Cyclooxygenase
Cox-1	Cyclooxygenase 1
Cox-2	Cyclooxygenase 2
Cox-3	Isoform of Cox-2 (therefore in brakes)
CRPC	Castration-resistant prostate cancer
CSES	Chronic stress escape strategy
CTGF	Connective tissue growth factor
Cx32	Connexin 32
CXC	CC chemokine receptors
CXCL1	Chemokine (C-X-C motif) ligand 1
CXCR2	C-X-C motif chemokine receptor 2, Interleukin 8 receptor, beta, IL8RB
CXCR4	C-X-C motif of chemokine receptor 4
CYP*	Cytochrome P450 isoform
CYP1A1	Cytochrome P450, family 1, subfamily A, polypeptide 1
D-1MT	Dextro-1-methyl tryptophan
DCIS	Ductal carcinoma in situ
DKK	Dickkopf Wnt signaling pathway inhibitor
D-Kyn	D-kynurenine
DOCK180	Dedicator of cytokinesis
DSS	Dextran sulfate sodium
DZNep	3-Deazaneplanocin A
E1A	Adenovirus early region 1A
E12/E47	E2A immunoglobulin enhancer-binding factors E12/E47, transcription factor 3 (TCF_3)
E2F4/5	Cytoplasmic complex of Smad3, retinoblastoma-like protein 1 (P107, RBL1), E2F4/5 and D-prostanoid (DP1)
E2F-DP	E2 promoter-binding–protein-dimerization partner
EBV	Epstein-Barr virus
E-Cadherin	CAM 120/80 or epithelial cadherin, cadherin-1, epithelial cadherin
ECM	Extracellular matrix
EGF	Epidermal growth factor
EGR1	Early growth response protein 1
EMT	Epithelial-mesenchymal transition
EPA	Omega-3 fatty acids eicosapentaenoic acid
ERK	Extracellular signal-regulated kinases, mitogen-activated protein kinase (MAPK)
ER-positive	Estrogen receptor positive
ESCC	Esophageal squamous cell carcinoma
EZH2	Enhancer of the zeste homolog 2
FADD	Fas-associated death domain
FAK	Focal adhesion kinase
FDA	Food and Drug Administration
Ficz	6-formylindolo (3,2-b) carbazole
FoxC1	Forkhead box C1
FOXO3a	forkhead box protein O3a
FSP1	Fibroblast-specific protein 1 (S100A4)
G3BP2	Ras GTPase-activating protein-binding protein 2
Gro-1	Growth-regulated purported oncogene 1
GSC	Homeobox protein goosecoid
GSK-3β	Glycogen synthase kinase 3β
GST	Glutathione-S-transferase
H_2S	Hydrogen sulphide
HATs	Histone acetyltransferases
HCB	Hexachlorobenzene
HCC	Hepatocellular carcinoma
HCECs	Human corneal epithelial cells
HDACs	Histone deacetylases
HGF	Hepatocyte growth factor (scatter factor)
Hox	Homebox gene
HPV	Human papillomavirus
Hsp90	Heat shock protein 90
IDC	Invasive ductal carcinoma
IDO	Indoleamine 2,3-dioxygenase
IDO1	Indoleamine-2,3-dioxygenase 1
IGF2	Insulin-like growth factor 2
IHC	Immunohistochemistry
IFγ	Interferon gamma
IL-6	Interleukin 6
IL-7	Interleukin 7
IL-8	Interleukin 8
IL-13	Interleukin 13
IL-21	Interleukin 21
IL-33	Interleukin 33
IL-β1	Interleukin beta 1
IPF	Idiopathic pulmonary fibrosis
IRE1	Inositol-requiring enzyme 1
ISC	Intestinal stem cell
JNK	c-Jun N-terminal kinase
KLF6	Krüppel-like factor 6
Kyn	Kynurenine
LINE1	Long interspersed nuclear element-1
LMP1	Latent membrane protein 1
Los	Losartan
LOX	Lysyl oxidase
LOXL2	Lysyl oxidase-like-2
LOXL3	Lysyl oxidase homolog 3

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
MAPK	Mitogen-activated protein kinase, extracellular signal-regulated kinase (ERK)
mCRPC	Metastasized castration-resistant prostate cancers
MDA	Malondialdehyde, propanedial
Meis1-3	DNA binding cofactors MEINOX for PBX and Hox with myeloid ecotropic viral integration site1-3
$Meis1_{27}$	Meis1d transcript with 27 kD weight
$Meis1_{32}$	Meis1d transcript with 32 kD weight
MEINOX	A contraction of MEIS and KNOX
MET	Mesenchymal-epithelial transition
miRNAs	microRNAs
miR21	micro RNA-21
MME	Macrophage metalloelastase, matrix metalloproteinase 12 (MMP-12)
MMP-1	Matrix metalloproteinase 1
MMP-2	Matrix metalloproteinase 2
MMP-3	Metalloproteinase 3 (stromelysin-1)
MMP-7	Matrix metalloproteinase 7, pump-1 protease, PUMP 1
MMP-9	Matrix metalloproteinase 9
MMP-12	Matrix metalloproteinase 12 (macrophage metalloelastase, MME)
MMP-13	Matrix metalloproteinase 13, collagenase 3
MMP-14	Matrix metalloproteinase 14 (MT1-MMP)
MMPs	Metalloproteinases
mTORC1	Rapamycin complex 1
MYOD1	Myogenic differentiation 1
NCCCT	Normal cell to cancerous cell transition
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NF-κB1	Nuclear factor kappa-light-chain-enhancer of activated B cells 1, protein 50 (p50) its progenitor protein 105 (p105)
NF-κB2	Nuclear factor kappa-light-chain-enhancer of activated B cells 2, protein 52 (p52) and its progenitor protein 100 (p100)
NKcells	Natural killer cells
NPC	Nasopharyngeal carcinoma
NSAIDs	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung carcinoma
OSM	Oncostatin-M
OSCC	Oral squamous cell carcinoma
$p27^{KIP1}$	Cyclin-dependent kinase inhibitor 1B
P38	P38 mitogen-activated protein kinases
p53	Tumor protein p53
p107	Retinoblastoma-like protein 1 (RBL1)
p120	protein 120, catenin delta-1
p130	Retinoblastoma-like protein 2 (RBL2)
p130(cas)	Breast cancer anti-estrogen resistance protein 1, BCAR1
P2RX7	P2X purinoceptor 7
p300	Histone acetyltransferase p300, adenovirus early region 1A (E1A)-associated protein p300
PAI1	Plasminogen activator inhibitor-1
PCB	Polychlorinated biphenyl
PCN	Precancerous niche
PDGF	Platelet-derived growth factor
PBX	Pre-B-cell leukemia transcription factor homeobox
PCs	Parietal cells
Pdcd4	Programmed cell death protein 4
PD-L1	Programmed death-ligand 1
PFL	Positive feedback loop
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
PGFF2α	Prostaglandine F2 alpha, (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enyl]cyclopentyl] hept-5-enoic acid
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	Phosphatidylinositide 3-kinase
PKC	Protein kinase C
PKM2	Pyruvate kinase M2
PKNOX1	PBX/Knotted 1 Homeobox 1
PPAR-γ	Peroxisome proliferator-activated receptor gamma
PRC	Polycomb Repressive Complex 2
PREP1-2	PBX-regulating protein-1-2
Pro-MMP-1	Pro-matrix metalloproteinase 1
Pro-MMP-7	Pro matrix metalloproteinase 7
Pro-MMP-9	Pro-matrix metalloproteinase 9
Prrx1	Paired related homeobox 1

PSCs	Pancreatic stellate cells
PTEN	Phosphatase and tensin homolog
PTTG1	Pituitary tumor transforming gene 1
PUMA	BH3-only protein
PUMP1	Pump-1 protease, matrix metalloproteinase 7, MMP-7
QUE	3,5,7,3′,4′-pentahydroxylflavone, Quercetin
Rac1	Ras-related C3 botulinum toxin substrate 1
RANTES	Chemokine (C-C motif) ligand 5, CCL5
RB	Retinoblastoma
RB1	Retinoblastoma protein 1
RB2	Retinoblastoma protein 2
RB1CC1	Retinoblastoma coiled coil protein 1
RBL1	Retinoblastoma-like protein 1 (p107)
RBL2	Retinoblastoma-like protein 2 (p130)
RelA	Transcription factor p65 encoded by RELA gene,
RelB	Transcription factor encoded by the RELB gene interacting with NF-κB
rHBs	Hepatoblasts
RhoA	Ras homolog gene family, member A
Rnf43	Really interesting new gene (ring) finger protein 43
ROS	Reactive oxygen species
S1P	Sphingosine-1-phosphate
SIP1	Survival of motor neuron protein-interacting protein 1
Sine	Short interspersed elements
SLC16A12	Solute carrier family 22 (organic anion/ cation transporter), member 12
SLK	STE20-like serine/threonine-protein kinase
Slug	Zinc finger protein SNAI2
SNAI1	Zinc finger protein SNAI1 (Snail)
SNAI2	Zinc finger protein SNAI2 (Slug)
Snail	Zinc finger protein SNAI1
SOX	Sry-related high-mobility-group Box
SOX11	Transcription factor SOX-11
SP1	Specificity protein 1
SphK	Sphingosine kinase isoform
Src	Proto-oncogene tyrosine-protein kinase
SPRY1	Protein sprouty homolog 1
SPRY2	Protein sprouty homolog 2
Sry	Sex-determining region Y
Syk	Spleen tyrosine kinase
STAT3	Signal transducer and activator of transcription 3
TALE	Three-amino acid extension loop protein
TBET	T-box transcription factor
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TCF_3	Transcription factor 3, E2A immunoglobulin enhancer-binding factors E12/E47
TDO	Tryptophan-2,3-dioxygenase
TGF-β1	Transforming growth factor beta 1
THBS1	Thrombospondin 1
TIMPs	Tissue inhibitors of metalloproteinases
TIMP-1	Tissue inhibitor of metalloproteinases-1
TIMP-2	Tissue inhibitor of metalloproteinases-2
TNC	Tenascin-C
TNFα	Tumor necrosis factor alpha
TNFR1	Death type 1 TNF receptor
TPA	12-*O*-tetradecanoylphorbol-13-acetate
TRADD	TNF receptor-associated death domain
Twist1	Twist-related protein 1
TXA2	Thromboxane A2, (Z)-7-[(1S,2S,3R,5S)-3-[(E,3S)-3-hydroxyoct-1-enyl]-4,6-dioxabicyclo[3.1.1]heptan-2-yl]hept-5-enoic acid
UGT	Uridine glucuronosyltransferases
VEGF	Vascular endothelial growth factor
WNT5A	Wnt family member 5a
XBP1	X-box binding protein 1
XRE	Xenobiotic responsive element (AAH response element, AHRE)
ZEB1	Zinc finger E-box-binding homeobox 1
ZEB2	Zinc finger E-box-binding homeobox 2
Znrf3	Cell-surface transmembrane E3 ubiquitin ligase zinc and ring finger 3, homologue of Rnf3

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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 origi-

nal material that has not previously been published. Both authors contributed to the discussion on its contents and approved the manuscript.

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