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Special Issue: Disruption of homeostasis-induced signaling and crosstalk in the carcinogenesis paradigm "Epistemology of the origin of cancer"
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REVIEW ARTICLE OPEN ACCESS

Metformin alters signaling induced crosstalk and homeostasis in the carcinogenesis paradigm "Epistemology of the origin of cancer"

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Abstract – The anti-hyperglycemic drug, Metformin, is effective in treating early stages of diabetes and has been associated with a 37% decrease in cancer incidence. While the precise mechanisms for the anti-cancer effects of Metformin remain to be elucidated, this review shows the multiplicity of its effects on interdicting signaling and crosstalk, anti-inflammatory effects and in restoring homeostasis, which, taken together, go beyond its well-known anti-hyperglycemic effect that serves as the basis for its use in type 2 diabetes. Metformin is much more than a one-trick pony. The recent discovery of several signaling pathways influenced by Metformin appears to have potential value in cancer therapy. Based on what we know at present, Metformin promotes beneficial effects attributed to its anti-inflammatory and anti-fibrotic effects largely demonstrated in vitro. Metformin activates or upregulates while it simultaneously inhibits or downregulates multiple signaling pathways of cell-cycle arrest and apoptosis accompanied by oxidative stress, which are in accordance with the 6-step sequence of carcinogenesis. Furthermore, in vivo studies in laboratory animals and in cancer patients are beginning to address the magnitude of the anti-cancer effects and delineate its anti-cancer effects. In this context, results from prior pancreatic and non-pancreatic cancer trials, which contained a significant proportion of the patient population treated with Metformin, will have to be reexamined in light of the observed anti-cancerous effects to gain additional insights. The detailed exploration of Metformin in the context of the "*Disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm Epistemology of the origin of cancer*" can provide helpful insights into the anti-proliferative mechanisms and could play a relevant role in anti-cancer therapy in the future.

Keywords: Akt, ALL, ALK-1, AMP, AMPK, Apoptosis, Autophagy, Bax, Bcl-2, BrDU, Breast cadherin, Cancer, Carcinogenesis, Cell transition, Chronic inflammation, Collagen, Collagenase, Colon, CCC, Cox-1, Cox-2, CRP, CXCL8, Decorin, Diabetes, DNA, EGFR, Elastin, Elastase, Endometrium, Epidemiology, Epigenetics, Erk, Fibronectin, Fibrosis, FOXO3a, Genetics, Genomics, GRIM-19, GTPase, HCC, HER2/neu, HIF-1α, HPV, Interleukin, Keratin, Keratinase, KRAS; liver, LOX, MAPK, MCP1, Metastasis, Metformin, Microbiome, microRNA, MMP, mTOR, mTORC1, Mutation, NF-κB, NLRP3, NRF-2, NSCLC, Ovary, PAI-1, PARP, Pathogenesis, PCK, PEPCK, PGE2, PPA2, Precancerous niche, Proteomics, Pyroptosis, RNA, Signaling, Snail, Somatic mutation theory, STAT3, T2D, TGF, TIMP1, Vimentin, Virus

Introduction

An exploration of the potential ant-cancer effects of Metformin must necessarily begin with an understanding of type 2 diabetes (T2D) and the epidemic of obesity, the latter also a recognized risk factor in several cancers. The proportion of people above 60 years old will increase from 841 million at present to an estimated 2 billion by 2050 according to the World Health Organization [1]. This will increase the burden of age-related chronic diseases such as cancer, neurologic and cardiovascular diseases and T2D as *the* global costs for healthcare worldwide [2]. The increase in metabolic syndrome, defined by three out of five medical conditions, which include obesity, elevated blood pressure, insulin resistance, elevated fasting plasma glucose, high serum triglycerides, and low levels of high-density cholesterol (HDL), is a risk factor for T2D [3] and explains the parallel increase of T2D prevalence in the US [4], Asia [5], Europe [6], and the Middle East [7] reflecting global healthcare liabilities. T2D is associated with morbid obesity and some 35% (78.6 million) of US adults are obese [8].

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Recently, an increase of gestational diabetes from 7.4% to 14.1% within the US over an 11 year period was reported [9]. An estimated 40% of the US population is at risk of developing T2D, and the corresponding percentage in Blacks or Hispanics within the US is thought to be as high as 50% [10]. A 10% increase in the prevalence of T2D in patients between 40 and 74 years of age in individuals with a body mass index (BMI) $\geq$ 30 kg/m^2 was reported [11]. "*In high-income countries, reduction in non-tobacco cardiovascular disease and diabetes mortality contributed most to gains in life expectancy at age 60 years between 1980 and 2011*" [12] but the trend of growth in morbid obesity with its developing T2D may can counteract or reverse this effect within the future.

A European scenario, based on current and past BMI trends, revealed that morbid obesity is expected to increase in 53 European countries through 2030 with the highest prevalence in Greece, the United Kingdom, and Slovakia [6].

The interaction of the microbiome and morbid obesity in relation to cancer is reviewed elsewhere in this special issue [13]. Increased cancer rates associated with diabetes are reported for breast cancer, colorectal cancer, liver and pancreatic cancers, bladder cancer, and endometrial cancer [14], while the risk of developing prostate cancer is paradoxically decreased [15, 16].

Understanding the interaction of the microbiome with morbid obesity in the context of signaling and crosstalk together with the apparent beneficial effects of Metformin will enhance our understanding of carcinogenesis and of the effectiveness of Metformin in cancer therapy.

Metformin

Metformin is a biguanid (1,1-Dimethylbiguanid) used in the management of T2D (National Institute of Health) [17]. The exact mechanism of action of Metformin is not fully understood. Over the past decade, Metformin has been shown to reduce cancer risk by about 37% [18]. The incidence of intrahepatic cholangiocellular carcinoma (CCC) was reduced by about 60% in Metformin-treated T2D patients [19].

In a rat model, it was shown that Metformin blocks testosterone which also explains why Metformin might be useful in treating polycystic ovarian syndrome (PCOS) [20–22]. However, at present PCOS is an off-label use for Metformin [23].

A study using patient-derived xenograft (PDX) lines from two colorectal cancer patients for assessing Metformin and 5-fluorouracil (5-FU) showed that Metformin inhibited tumor growth by at least 50% after 24 days and, when combined with 5-FU, tumor growth was inhibited by as much as 85% [24]. Metformin can reduce the growth of mammary cancer cells in mice, which also shows its anti-metabolic effects [25]. The experiment showed that modulated microRNA contributes to both the metabolic as well as the anticancer effects of Metformin. In this connection, Metformin results in increased expression of Dicer, an endoribonuclease responsible for cutting double-stranded ribonucleic acid (RNA) into shorter double-stranded fragments. When Dicer was eliminated in knock-out mice, these effects were suppressed. Metformin also downregulates messenger RNAs (mRNAs) such as c-MYC, insulin-receptor substrate 2 (IRS-2) and hypoxia-inducible factor-1 alpha (HIF-1α). The regulation of c-MYC requires adenosine monophosphate (AMP) signaling and the upregulation of the microRNA (miRNA) precursor, miR33 [26].

Metformin and microbiome

Metformin influences the composition of the intestinal flora by increasing anaerobic gram-negative bacteria, *Akkermansia,* and mucin-producing goblet cells [27]. Otherwise, the Metformin-microbiota interactions are varied: *Houttuynia cordata extract* (HCE) together with Metformin influences the composition of the gut microbiota by decreasing Gram-negative bacteria [28]. Metformin can increase and trigger the abundance of opportunistic pathogens with dysbiosis [29] and thus Metformin can induce changes in signaling as well as inducing altered microbiota signatures [30–37]. Typically diet and fat metabolism influences the microbiome composition [38–41].

Genes for fatty acid metabolism of triglycerides, HDL, and insulin pathways are regulated by miR33 [42]. miR33 binds to the tumor suppressor gene, p53, resulting in activation of apoptosis [43]. Metformin downregulates miR-21 through the transforming growth factor beta 1 (TGF-β1) pathway such that overexpression of miR-21 abrogates Metformin-mediated inhibition of the protein kinase B (PKB, Akt), SMAD, and extracellular signal–regulated kinases (ERKs) signaling pathways and can abolish the inhibitory effects of Metformin-induced protein phosphorylation [44].

Activin receptor-like kinase 1 (ALK-1) signaling inhibits lymphatic vessel formation [45] and mediates angiogenesis in solid tumors, which serves as a basis for using it as a target in cancer therapy [46, 47]. Metformin also activates AMP activated protein kinase (AMPK), inhibiting ALK-1 mediated angiogenesis [48, 49] but it appears that Metformin has a short-term paradoxical effect by increasing pro-angiogenic mediators [50]. This needs further study for clarification.

Metformin and apoptosis

Metformin is known to induce apoptosis [51–53] but can block methylglyoxal (MG)-induced apoptosis in neuronal cells [54]. In pancreatic cancer cells, Metformin induces apoptosis in a dose-dependent manner through activation of caspase-3, -8, and -9 and poly-ADP-ribose polymerase (PARP) cleavage [55]. Furthermore, Metformin induces apoptosis in lung [56] and colon cancers [57, 58].

Metformin was shown to induce the inflammatory form of apoptosis, pyroptosis, in esophageal squamous cell carcinoma (ESCC) via proline-, glutamic acid- and leucine-rich protein-1 (PELP1) and miR-497 [59]. Apoptosis is also inhibited by Metformin in melanoma [60]. On the other hand, Metformin has been reported to decrease chemotherapy induced apoptosis [61]. However, this effect seems to be

dependent on whether or not hypoxic conditions are present as Metformin was shown to be limited in its ability to activate AMPK and inhibit mTOR signaling in hypoxic pediatric sarcomas [62]. Typically, large tumors have a higher rate of central hypoxic conditions [63, 64], and the Metformin effect could be dependent on the hypoxic and/or central necrotic areas within the tumor.

Scientists from Brazil and Canada investigated the molecular mechanisms for the observed anti-cancer effects of Metformin by assessing its ability to induce apoptosis and cell cycle arrest [65]. Metformin was administered at 24, 48, and 72 h in vitro in an established breast cancer cell line (MCF-7, American Type Culture Collection, Middlesex, United Kingdom). The controls used a carcinoma cell line and rats (LLC WRC-256 Walker rats). Bromo-deoxyuridine (=bromo-2'-deoxyuridine, BrDU) as the pyrimidine analog of thymidine can be selectively incorporated into deoxyribonucleic acid (DNA) during the S-phase of the cell cycle so that BrDU can be used for the identification of DNA-synthesis in cells, smears, and tissue probes. Specific monoclonal antibodies against BrDU allow assessment of DNA-synthesis and of cell kinetics and cell proliferation. Metformin decreased the activation of insulin receptor β (IRβ), Akt, and extracellular signal-regulated kinase 1 (Erk1, mitogen-activated protein kinase 3, MAPK3)/extracellular signal-regulated kinase 2 (Erk2, mitogen-activated protein kinase 1, MAPK1) in mice followed by increased phosphorylated AMPK (pAMPK), forkhead box O3 (FOXO3a), cyclin-dependent kinase inhibitor 1B (p27), B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax) and cleaved caspase-3. This was associated with decreased phosphorylation of ribosomal protein S6 kinase beta-1 (p70S6 K) and B-cell lymphoma 2 protein (Bcl-2) expression with consequent increase of phosphorylated p38 mitogen-activated protein kinases (MAPKs), catalase, manganese-dependent superoxide dismutase (MnSOD, SOD2) and superoxide dismutase 1 (SOD1, Cu-Zn SOD) protein expression, and an anti-proliferative effect by inducing apoptosis and cell cycle arrest mediated via AMPK and FOXO3a. Furthermore, Metformin increases carcinoma cell apoptosis and senescence in stromal cells [66].

Metformin and inflammation

The significance of chronic inflammation in carcinogenesis has been reviewed [67]. In addition, an anti-inflammatory effect of Metformin was shown through the reduction of C-reactive protein (CRP), a marker of inflammation [68]. In human ovarian SKOV3 and HO-8910PM cell lines, Metformin inhibited proliferation and adhesion in a dose-dependent manner and decreased cancer cell growth and metastasis in vivo [69], along with the plasminogen activator inhibitor-1 (PAI-1) [70].

A randomized, placebo-controlled trial with T2D patients treated with insulin plus either Metformin or placebo showed that the addition of Metformin resulted in a reduction of von Willebrand factor (vWF), soluble vascular adhesion molecule-1 (sVCAM-1), tissue-type plasminogen activator (t-PA), PAI-1, CRP, and soluble intercellular adhesion molecule-1 (sICAM-1) [71]. Typically, Metformin triggers AMPK-endothelial nitric oxide (NO) synthase (eNOS)-mediated signaling which has cardioprotective effects and a 34% decrease in cardiovascular morbidity and mortality in patients with myocardial infarction [72].

Recently, the anti-inflammatory effects of Metformin were further elaborated. Interleukin 8 (IL-8, C-X-C motif ligand (CXCL) 8, CXCL8) is increased in certain cancers such as stomach [73], breast [74, 75], pancreas [76], prostate [77], and colon [78] and these cancers are known to recruit inflammasome cells such as neutrophil granulocytes, monocytes and leukocytes [79]. Using the HEK293/TLR4 cell line, Metformin administration decreased the cell migration by "*lipopolysaccharide (LPS) induced CXCL8 expression in a dose-dependent manner through inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)*" [80].

Metformin and fibrosis with its remodeling - precancerous niche (PCN)

The signaling and crosstalk of remodeled fibrosis by chronic inflammation and its induction of a precancerous niche (PCN) has been reviewed [81]. Metformin protects against radiation-induced pneumonitis and fibrosis [82, 83] which was reported in liver cells and found to be associated with the mechanistic target of rapamycin (mTOR)/HIF-1α inhibition [84].

Thrombospondin-1 (TSP-1) is increased by Metformin via NF-κB and Erk1/2/extracellular signal-regulated kinase 5 (Erk5, mitogen-activated protein kinase 7, MAPK7) pathways and thus decreases angiogenesis [85]. Metformin decreases hypoxia-induced angiogenesis by decreasing HIF-1α and angiogenesis-associated factors (AAFs) [86, 87].

Metformin downregulates the structural proteins Col3α, Col6α, elastin and the collagen cross-linking enzyme, lysyl oxidase (LOX), tumor necrosis factor alpha (TNFα), IL-6, monocyte chemoattractant protein 1 (MCP1, chemokine (C-C motif) ligand 2, CCL2) and epidermal growth factor (EGF)-like module-containing mucin-like hormone receptor-like 1 (EMR1, F4/80) which is an indicator of macrophages recruitment, and also inhibits HIF-1α activation-induced fibrosis and inflammation in adipose tissue [88]. Metformin abrogates receptor tyrosine-protein kinase erbB-2 (HER2/neu, cluster of differentiation 340, CD340) signaling-induced tumor angiogenesis by inhibiting VEGF secretion and reduces micro-vessel density [89–92].

Metformin suppresses the inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ, inhibitor of nuclear factor kappa-B kinase 2, IKK2) and also inhibits chemokine (C-X-C motif) ligand 1 (CXCL1) [93], downregulates chemokine (C-X-C motif) ligand 10 (CXCL10), tissue inhibitor of metalloproteinase 1 (TIMP1) [94], and inhibits PAI-1 [70]. As Metformin inhibits PAI-1, it also inhibits the creation of the PCN and thereby can affect the transition of a normal cell to a cancer cell. As TIMP-1 promotes liver metastasis [95], this pathway might also be interdicted by Metformin.

Metformin: leptin, STAT3, and adenosine monophosphate (AMP) activated protein kinase (AMPK)

Metformin increases leptin sensitivity in rats fed a high fat diet which suggests that Metformin could be effective in treating obesity [96]. Metformin treatment resulted into an increase of transcription factor signal transducer and activator of transcriptor 3 (STAT3). However, intracerebroventricular leptin investigations of anorexic and fat-losing effects showed that lower leptin doses were required to induce these effects in Metformin-treated high-fat fed obese rats than in untreated rats, suggesting that anorexic and fat-losing effects of leptin were enhanced by Metformin. Leptin decreased hypothalamic pAMPK levels, which were not observed by Metformin treatment. Intracerebroventricular injections of Metformin in another animal model decreased food intake with an increase of cyclic AMPK (cAMPK) and STAT3 but increasing the Metformin dosage did not have an effect on a further pAMPK or STAT3 increases leading to the inference that Metformin may be helpful in the treatment of mild-to-moderate obesity [97]. These effects of Metformin are relevant as obesity is a risk factor for several cancers [13].

Hepatic gluconeogenesis is inhibited by Metformin through the activation (phosphorylation) of AMPK [98, 99]. Recently, this mechanism was revised to include that Metformin antagonizes glucagon through AMP accumulation in mouse hepatocytes where it inhibits adenylate cyclase with suppression of a glucagon-induced increase of cyclic adenosine-monophosphate (cAMP) with protein kinase A (PKA). These effects result in the inhibition of glucagon-dependent glucose output from hepatocytes with a corresponding decrease in blood glucose [98, 100]. Furthermore, the inhibition of gluconeogenesis by suppression of the mitochondrial glycerophosphate-dehydrogenases has been elucidated [101].

Transgenic mice treated with Metformin showed an increase of AMPK activity with inhibition of mTOR [102]. Metformin inhibits hepatic mammalian target of rapamycin complex 1 (mechanistic target of rapamycin complex 1, mTORC1) signaling by dose-dependent mechanisms through adipocyte AMPK and the tuberous sclerosis complex (TSC) [103] but this inhibition also occurs via an AMPK-independent pathway [104, 105]. This pathway may also be triggered by Ragulator-Rag complex (RAG) guanosine triphosphate hydrolase (GTPase) independently from TSC/mTOR/AMPK [106]. Inhibition of the mTOR effector, p70S6K1, was associated with a decrease in human HER2/neu inhibiting breast carcinoma cell growth ([107 *reviewed in* 108]).

In contrast to the obese animal model discussed above [96, 97], Metformin inhibits cell transition and metastasis by decreasing cyclooxygenase-2 (Cox-2)/prostaglandin E2 (PGE2)/STAT3 signaling in prostate cancer cells [109]. Here, inactivating Cox-2 abolished Metformin effects while PGE2 administration increased STAT3 and cell transition. The combined treatment with Metformin and aspirin in liver cancer HepG2 cells downregulated pAMPK and mTOR with consecutive induction of apoptosis and G2/M cell arrest. Investigation of hepatocellular carcinoma (HCC) specimens showed increased pAMPK, mTOR and β-catenin compared to cirrhotic liver tissue controls [110]. Furthermore, Metformin sensitized sorafenib therapy suppressing cell proliferation and transition with promoting apoptosis presumably by decreasing insulin resistance [111]. In cancer stem cells, the Metformin effect was dependent on AMPK-mTOR and glutamine metabolism [112].

The human enzyme phosphoenolpyruvate carboxykinase (PEPCK, PCK) has a cytoplasmic (PCK1, PEPCK-C) and mitochondrial isoform (PCK2, PEPCK-M); PCK is a key enzyme for (1) gluconeogenesis, (2) glyceroneogenesis, (3) serine synthesis and (4) conversion of the carbon skeletons of amino acids. PCK converts oxaloacetate into phosphoenolpyruvate and carbon dioxide and serves as a cataplerotic enzyme resulting into anabolic metabolism ([113–115 *reviewed in* 116]). Corticoids and cAMP increase, while insulin negatively regulates PCK [117]. However, over 80% of tumors and 78% of non-tumor tissue express PCK1 while investigations using colon cancer cell lines revealed an overexpression by ~17% [118] and mitochondrial PCK2 was overexpressed in thyroid, bladder, breast, kidney, and non-small-cell lung cancer (NSCLC) [119]. In contrast, PCK1 and PCK2 are downregulated in HCC, rarely mutated in HCC, and forced PCK1 expression suppresses liver cancer growth in HCC [120, 121]. PCK1 activates pAMPK with suppression of cell proliferation and growth, and Metformin as an AMPK activator suppresses HCC growth [122].

Furthermore, another dysregulation of homeostasis is found in HCC: 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is downregulated while 11β-HSD2 is upregulated which can be reversed by dexamethasone [120] and here Metformin shows yet another effect by increasing 11β-HSD1 in morbid obesity [123].

In a study of sugar uptake, Onodera et al. [124] demonstrated that overexpression of glucose transporter type 3 (GLUT3) in non-malignant human breast cells activated known oncogenic signaling pathways including epidermal growth factor receptor (EGFR), β1 integrin, mitogen-activated protein kinase kinase 2 (MAPK2, MEK), and Akt, leading to a loss of tissue polarity and increased growth. Conversely, reduction of glucose uptake in malignant cells facilitated the formation of normal cell growth with basal polarity and suppressed oncogenic pathways. Loss of epithelial integrity involved activation of Ras-related protein 1 (Rap1, Ras-proximate-1) via exchange protein directly activated by cAMP – exchange factor directly activated by cAMP 1, exchange factor directly activated by cAMP 1 (EPAC1, Rap guanine nucleotide exchange factor 3, RAPGEF3) –, involving O-linked N-acetylglucosamine modification downstream of the hexosamine biosynthetic pathway, mediated by pyruvate kinase M2 (PKM2) and soluble adenylyl cyclase (sAC), respectively. The authors state, "*Unexpectedly and importantly, we found that unlike reported literature, in 3D the differences between "normal" and malignant phenotypes could not be explained by HIF-1α, AMPK or mTOR pathways.*" The extent to which

Metformin might directly affect these specific pathways is not well understood but these studies illustrate the importance of 2D versus 3D cell assays and suggest targets for future studies.

Metformin in *Porphyromonas gingivalis* (P.g.)-infected streptozotocin (STZ)-induced diabetic mice was shown to suppress the inflammasome by inhibiting NIMA-related kinase 7(Nek7)/NOD-like receptor family pyrin domain containing 3 (NLRP3) expression independently of mTOR [125].

Metformin and cell transition

Cell transition during carcinogenesis is complex [126]. The observed inhibition of cell-cell transition by Metformin likely works through multiple pathways. Metformin is an activator of AMPK and also suppresses cell transition via inhibition of reactive oxygen species (ROS) mediated by induction of heme oxygenase-1 and the endogenous antioxidant, thioredoxin [127]. Metformin was shown to inhibit cell transition in prostate cancer cells by inhibiting TGF-β, N-cadherin, vimentin and epithelial Cadherin (E-cadherin, cadherin-1, CAM 120/80) and β-catenin at mRNA and protein levels [128]. This may also be associated with upregulation of miR30a and downregulation of the [sex-determining region Y (Sry) box-containing] transcription factor 4 (SOX4).

Metformin inhibits TGF-β1-induced cell transition via pyruvate kinase M2 (PKM2) relative-mTOR and p70s6 k signaling [129]. On the one hand, high glucose itself induces downregulation of the mitochondrial gene associated with retinoid-IFN-induced mortality 19 (GRIM-19, NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 13, NDUFA13) with activation of STAT3 signaling resulting in cell proliferation [130]. In this regard, Metformin did not have an effect on phosphorylated STAT3 levels in the HeLa cells, but decreased STAT3 levels in myoblast H9C2 cells.

Metformin inhibits IL-6-induced cell transition which may be related to the blocking of STAT3 phosphorylation [131]. Metformin also inhibits the nuclear translocation of NF-κB and phosphorylation of STAT3 [132] and the Janus kinase (JAK), STAT3, c-MYC signaling axis [133–135]. By downregulating STAT3, Metformin promotes autophagy [136] as discussed earlier [67]. Knockdown of TGF-β1 plus Metformin in a canine mammary cancer xenograft model decreased cell transition and metastasis (cell line, CF41) [137].

Metformin application to the human AGS gastric cancer cell line showed decrease of vimentin, β-catenin, and induction of E-cadherin [138]. Using a human cholangiocarcinoma cell line, HuCCT1, plus Metformin, showed downregulation of the anti-apoptotic protein, Bcl-2, and induced myeloid leukemia cell differentiation protein (Mcl-1), cadherin-2 (N-cadherin, neural cadherin), zinc finger protein SNAI1 (Snail), and matrix metalloproteinase-2 (MMP-2, gelatinase A) as well as decreased STAT3 activation together with increased of E-cadherin expression [139]. It was also demonstrated earlier that Metformin increases E-Cadherin while decreasing matrix metalloproteinase-9 (MMP-9, gelatinase B)) expression [140].

Metformin downregulates/decreases IRβ, Akt, IKKβ, CXCL1, CXCL10, TIMP1, vWF, PAI-1, mTORC1 signaling by dose-dependent mechanisms through adipocyte AMP-activated protein kinase (AMPK) and the TSC Complex, NF-κB, CRP, miR-21 through the TGF-β pathway, c-MYC, IRS-2, HIF-1α, Col3α, Col6α, Elastin, LOX, TNF-α, IL-6, MCP1, TGF-β1 via PKM2 relative-mTOR/p70s6 k signaling, Cox-2/PGE2/STAT3 signaling, STAT3 and its phosphorylation, EMR1, microvessel density, JAK/STAT3/c-MYC pathway, vimentin, β-catenin, Bcl-2, Mcl-1, N-cadherin, Snail, MMP-2, MMP-9, and ROS via induction of heme oxygenase-1 and endogenous antioxidant thioredoxin (Fig. 1). Otherwise Metformin upregulates/activates E-cadherin, Dicer, sVCAM-1, t-PA, sICAM-1, p-AMPK, FOXO3a, p70S6 K, and IL-8 (expression in a dose-dependent manner through inhibiting NF-κB), and increases TSP-1 via NF-κB and Erk1/2/Erk5.

Metformin and clinical trials

Searching the US National Library of Medicine from the National Institute of Health (NIH) on Feb 20, 2019 for the variables "*metformin*" and "*cancer*" and "*trial*", yielded $n = 315$ documented trials independent from its active status or various entities [141].

The detailed signaling and crosstalk resulting from a pathogenic stimulus and which evokes the chronic inflammation involved in morbid obesity had been reviewed earlier (*reviewed in* [13, 67]). This is of significance in neurological diseases such as Parkinson or dementia as well (*reviewed in* [142]). Metformin is increasingly becoming recognized for decreasing the inflammasome. Recently, a matched-pair retrospective cohort trial in 15,676 individuals from Taiwan investigated the dementia risk in T2D and Metformin: "*The overall hazard ratios suggested a significantly lower risk of dementia associated with metformin use in either the unmatched cohort or the matched cohort. In tertile analyses, the hazard ratios suggested a reduced risk in a dose-response pattern*" [143].

In 2005, a case-control study from Tayside in Scotland evaluated 314,127 T2D patients and selected 11,876 who were newly diagnosed with diabetes. From this pool, 923 patients who had been admitted to a hospital with a cancer diagnosis were selected [144]. Two randomized control cases were selected for each Metformin case and were matched for age, year of diagnosis, and gender. The study concluded that the administration of Metformin reduced cancer risk in T2D patients, including in patients with breast [145], prostate [146] and colon cancers [98].

In a study of 123 acute lymphoblastic leukemia (ALL) patients treated with and without Metformin, the overall survival at a median follow up of 700 days of follow-up was 43%, with a disease-free survival of 47%. Patients with Metformin had a lower rate of relapse compared to the

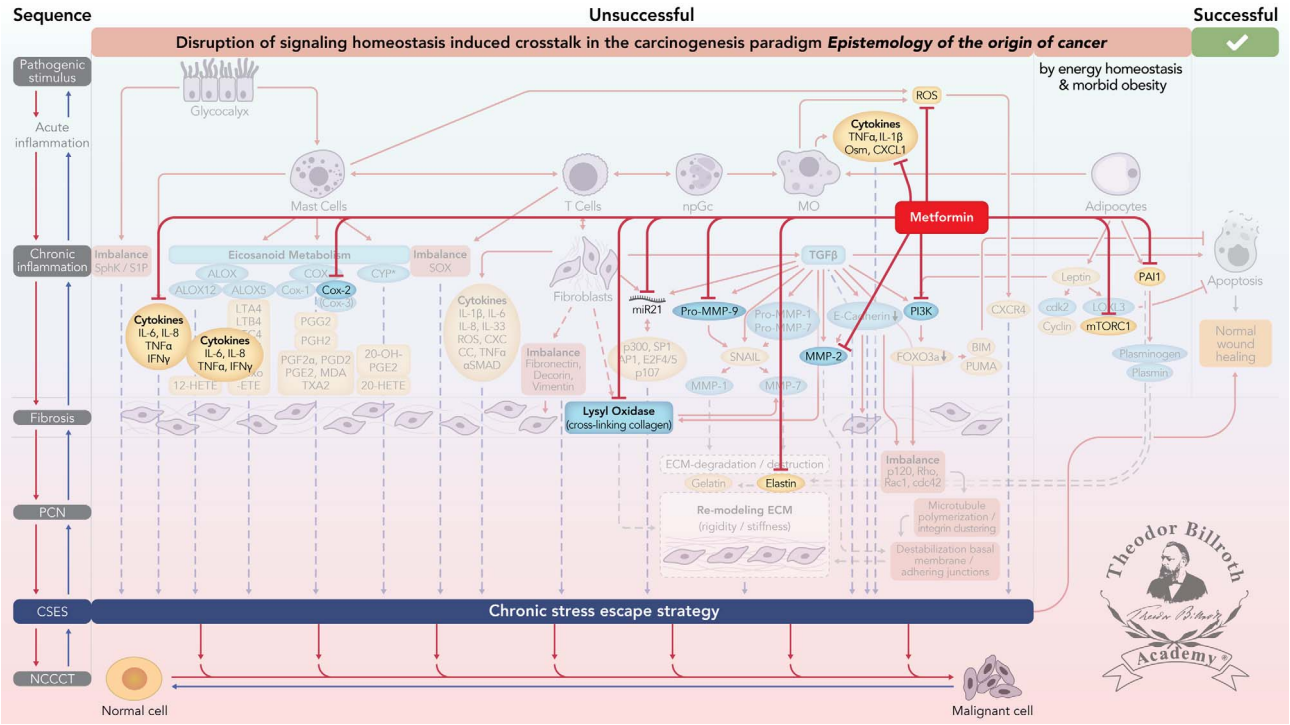

Figure 1. Metformin alters signaling induced crosstalk and homeostasis in the carcinogenesis paradigm "Epistemology of the origin of cancer" modified in accordance to Figure 1 published in this special issue [67]. Simplified scheme of the disruption of signaling homeostasis-induced crosstalk in the carcinogenesis 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 that 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 [67]. 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". 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", paper 6 "Precancerous niche (PCN), a product of fibrosis with remodeling by incessant chronic inflammation", paper 7 "Metformin alters signaling homeostasis", paper 8 "Transition from normal to cancerous cell by precancerous niche (PCN) induced chronic cell-matrix stress" and paper 9 "NF-κB signaling and crosstalk during carcinogenesis". *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; **IFNγ**: 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

group receiving only chemotherapy (6.5% vs. 17.1%, $P = 0.006$). The addition of metformin to the conventional treatment of ALL was associated with an improvement in survival, this association being independent of the type of biological risk at diagnosis [147].

Adding Metformin to simvastatin in PCOS increased therapeutic efficacy from 66.7% to 92.6%. In this study, efficacy was defined >15% decrease in the baseline values with regard to ovarian size, luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio, and lipid profile [148]. In an in vitro study using HT29 colon cancer cells, treatment with different concentrations of Metformin demonstrated growth inhibitory effects by increasing both apoptosis and autophagy; moreover, Metformin affected the survival of cultured cells by inhibiting the transcriptional activation of nuclear factor (erythroid-derived)-like 2 (NRF-2, NFE2L2) and NF-κB. Importantly, the effects were dose- and time-dependent. These results are very intriguing since Metformin is emerging as a multi-faceted drug with a good safety profile and low cost and might be a promising candidate for the prevention or the treatment of colorectal cancer [58, 149].

In a recent study (The METTEN study) to assess the efficacy of adding Metformin to neoadjuvant chemotherapy plus trastuzumab in early HER2/neu-positive breast cancer (BC). Women with primary, non-metastatic HER2/neu-positive BC were randomized (1:1) to receive Metformin (850 mg twice-daily) for 24 weeks concurrently with 12 cycles of weekly paclitaxel plus trastuzumab, followed by four cycles of 3-weekly FE75C plus trastuzumab (arm A), or equivalent regimen without Metformin (arm B), followed by surgery. Primary endpoint was the rate of pathological complete response (pCR) in the per-protocol efficacy population. The pCR rate was numerically higher in the Metformin-containing arm A (19 of 29 patients [65.5%, 95% CI 47.3–80.1]) than in arm B (17 of 29 patients [58.6%, 95% CI 40.7–74.5]; OR 1.34 [95% CI 0.46–3.89], $P = 0.589$). The rate of breast-conserving surgery was 79.3% and 58.6% in arm A and B ($P = 0.089$), respectively [150].

In a study of 101 women to assess whether Metformin prevented tamoxifen-induced endometrial changes and insulin resistance (IR) after a diagnosis of breast cancer, Metformin inhibited tamoxifen-induced endometrial changes and had favorable metabolic effects [151]. Application of 1500 mg metformin in a neoadjuvant setting revealed decreased insulin receptor (IR)-mediated and phosphatidylinositide 3-kinase (PI3 K) and Ras-MAPK signaling with less phosphorylation of Akt, Erk1/2 and acetyl coenzyme A carboxylase (ACC) [152].

In patients with endometrial cancer, Metformin was given preoperatively and reduced the serine/threonine phosphatase protein phosphatase 2A (PP2A) by immunohistochemistry and mRNA expression of the PP2A regulatory subunit, serine/threonine-protein phosphatase 2A regulatory subunit B (PPP2R4) measured by RT-PCR. Insulin resistance and diabetes are associated with PP2A [153, 154]. Knockdown of PPA2 in drosophila resulted in increased apoptosis [155] and abolished Erk negative regulating effects [156]. Inhibition of PPA2 by the microbial toxin okadaic acid (OA) activated p53 in T51B rat liver epithelial cells [157] and PP2A holoenzymes activated Akt and Erk signaling [158]. PPA2 and cyclin-Dependent Kinase 5 (CDK5) are independent prognostic factor in patients with gastric cancer [159]. Inhibiting PPA2 through the small molecule phosphatase inhibitor, LB-100, plus anti- programmed cell death protein 1(aPD-1) blockade activates mTORC1 signaling pathway [160]. The PP2A regulatory subunit, PPP2R4, decreases cell proliferation and activates caspases 3/7 increasing apoptosis in the human endometrial cancer cell lines HEC265 and HEC1B. Administering Metformin preoperatively in endometrial cancer patients reduces PP2A [161].

Anticancer effects were demonstrated by adding metformin in the therapy regimen in a small study of 25 patients with advanced or metastatic NSCLC: Metformin together with paclitaxel/carboplatin/bevacizumab improved progression free survival (PFS) by up to 47% compared to 15% in controls without improving median survival [162].

Furthermore, Metformin produced pro-apoptotic effects and enhanced the effectiveness of cisplatin specifically in KRAS/liver kinase B1 (LKB1, serine/threonine kinase 11, STK11) co-mutated patient-derived xenografts. Metformin also prevented the development of acquired tumor resistance to five consecutive cycles of cisplatin treatment (75% response rate with metformin + cisplatin as compared to 0% response rate with cisplatin), while reducing the number of CD133+ cells [163].

In a retrospective cohort of 87,344 patients with advanced prostate cancer, Cox proportional hazard analysis of overall survival showed improved survival in men with diabetes mellitus on Metformin (HR 0.82, 95% CI 0.78–0.86) compared to those with diabetes mellitus who were not on Metformin (HR 1.03, 95% CI 0.99–1.08). Hazard analysis of cancer-specific survival showed improved survival in men with diabetes mellitus on Metformin (HR 0.70, 95% CI 0.64–0.77) vs those with diabetes mellitus without Metformin (HR 0.93, 95% CI 0.85–1.00). The reference group was men with no diabetes mellitus [164].

In a small study of head and neck squamous cell carcinomas (HNSCC), Metformin was shown to differentially impact HNSCC subtypes with greater apoptosis in human papilloma virus negative (HPV−) HNSCC compared to

Figure 1. (Continued) 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.

human papilloma virus positive (HPV+) oropharyngeal squamous cell carcinoma. Moreover, the study presented the first in vivo human evidence that Metformin also triggers increased CD8 + Teff and FoxP3 + Tregs in the tumor microenvironment, suggesting an immunomodulatory effect in HNSCC [165]. In a double-blind, randomized, placebo controlled, multicenter study design, metformin in a daily dosage of 2,000 mg in Barrett's esophagus reduced serum levels of insulin and insulin resistance but were not associated with decrease of a biomarker of insulin pathway activation, phosphorylated S6 kinase (pS6K1), or alter epithelial proliferation or apoptosis in esophageal tissues [166].

Summary

The anti-hyperglycemic drug, Metformin, is effective in treating early stages of diabetes and is associated with a 37% decrease in cancer incidence. Several recent clinical studies show the benefits of Metformin as an adjuvant in anti-cancer therapy regimens. Metformin is much more than a one-trick pony. The recent discovery of several signaling pathways influenced by Metformin appears to be of potential value in cancer therapy. Based on what we know at present, Metformin promotes its ant-cancer effects in part due to its anti-inflammatory and anti-fibrotic effects demonstrated in vitro. The biguanid activates or upregulates while simultaneously inhibits or downregulates multiple signaling pathways involved in cell-cycle arrest and apoptosis which are accompanied by oxidative stress. The overall clinical and experimental data for the anti-cancer effects of Metformin are in accordance with the 6-step sequence of carcinogenesis. Further in vivo studies in laboratory animals and in cancer patients will address the magnitude of the anti-cancer effects of this widely used drug and delineate its anti-cancer effects with a long history of safety and low cost. In this context, results from prior pancreatic and non-pancreatic cancer trials which contain a significant proportion of the patient population treated with Metformin should be reexamined to tease out information of anti-cancer effects. Earlier results of applied anticancer therapies may have been masked within a subpopulation of patients who also received Metformin. The detailed exploration of Metformin in the context of the "*Disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm Epistemology of the origin of cancer*" on the one hand can provide significant insights into the anti-proliferative mechanisms and could play a relevant role in anti-cancer therapy in the future.

Nomenclature of abbreviations

5-FU	5-fluorouracil
5-oxo-ETE	(6E,8Z,11Z,14Z)-5-oxoicosa-6,8,11,14-tetraenoic acid
11β-HSD1	11β-hydroxysteroid dehydrogenase type 1
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
αSMAD	alpha-smooth muscle actin
AAFs	angiogenesis-associated factors
ACC	acetyl coenzyme A carboxylase
Akt	protein kinase B (PKB)
ALL	acute lymphoblastic leukemia
ALK-1	activin receptor-like kinase 1
ALOX	lipoxygenase, arachidonate lipoxygenase
ALOX5	5- lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase
ALOX12	12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type
AMP	adenosine monophosphate
AMPK	adenosine monophosphate (AMP) activated protein kinase
AP1	activator protein 1
Bax	B-cell lymphoma 2 (Bcl-2)-associated X protein
BC	breast cancer
Bcl-2	B-cell lymphoma 2 protein
BIM	B-cell lymphoma 2 protein (Bcl-2) interacting mediator of cell death
BMI	body mass index
BrDU	bromo-2'-deoxyuridine
cAMP	cyclic adenosine-monophosphate
cAMPK	cyclic adenosine monophosphate (AMP) activated protein kinase
CCC	cholangiocellular carcinoma
CCL2	chemokine (C-C motif) ligand 2, monocyte chemoattractant protein 1, MCP1
CD340	cluster of differentiation 340, receptor tyrosine-protein kinase erbB-2, HER2/neu
cdc42	cell division control protein 42 homolog
cdk2	cyclin-dependent kinase 2
CDK5	cyclin-dependent kinase 5
Cox	cyclooxygenase
Cox-1	cyclooxygenase 1
Cox-2	cyclooxygenase 2
Cox-3	isoform of Cox-2 (therefore in brakes)
CRP	C-reactive protein
CSES	chronic stress escape strategy
CXC CC	chemokine receptors
CXCL1	chemokine (C-X-C motif) ligand 1
CXCL10	chemokine (C-X-C motif) ligand 10
CXCR4	C-X-C motif of chemokine receptor 4
DNA	deoxyribonucleic acid
E2F4/5	cytoplasmic complex of Smad3, retinoblastoma-like protein 1 (P107, RBL1), E2F4/5 and D-prostanoid (DP1)
E-cadherin	CAM 120/80 or epithelial cadherin, cadherin-1,

EMR1	epidermal growth factor (EGF)-like module-containing mucin-like hormone receptor-like 1, F4/80
eNOS	endothelial nitric oxide (NO) synthase
EGFR	epidermal growth factor receptor
EPAC1	exchange factor directly activated by cAMP 1, Rap guanine nucleotide exchange factor 3, RAPGEF3
ERK	extracellular signal–regulated kinase
Erk1	extracellular signal-regulated kinase 1, mitogen-activated protein kinase 3, MAPK3
Erk2	extracellular signal-regulated kinase 2, mitogen-activated protein kinase 1, MAPK1
Erk5	extracellular signal-regulated kinase 5, mitogen-activated protein kinase 7, MAPK7
ESCC	esophageal squamous cell carcinoma
FOXO3a	forkhead box protein O3a
GLUT3	glucose transporter type 3
GTPase	guanosine triphosphate hydrolase
GRIM-19	retinoid-IFN-induced mortality 19, NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 13, NDUFA13
HCC	hepatocellular carcinoma
HCE	Houttuynia cordata extract
HDL	high-density cholesterol
HER2/neu	receptor tyrosine-protein kinase erbB-2, cluster of differentiation 340, CD340
HIF-1α	hypoxia-inducible factor-1 alpha
HNSCC	head and neck squamous cell cancer
HPV	human papilloma virus
IFNγ	interferon gamma
IKK2	inhibitor of nuclear factor kappa-B kinase 2, inhibitor of nuclear factor kappa-B kinase subunit beta (IKK-β)
IKK-β	inhibitor of nuclear factor kappa-B kinase subunit beta, inhibitor of nuclear factor kappa-B kinase 2, IKK2
IL-β1	interleukin beta 1
IL-6	interleukin 6
IL-8	interleukin 8 (chemokine (C-X-C motif) ligand CXCL 8, CXCL8)
IL-33	interleukin 33
IRβ	insulin receptor β
IRS-2	insulin-receptor substrate 2
JAK	Janus kinase
LB-100	small molecule phosphatase inhibitor
LH/FSH	luteinizing hormone/follicle-stimulating hormone
LOX	lysyl oxidase
LOXL3	lysyl oxidase homolog 3
LKB1	liver kinase B1, serine/threonine kinase 11, STK11
LPS	lipopolysaccharide
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
MAPKs	p38 mitogen-activated protein kinases
MAPK1	mitogen-activated protein kinase 1, extracellular signal-regulated kinase 2, Erk2
MAPK2	mitogen-activated protein kinase 2
MAPK3	mitogen-activated protein kinase 3, extracellular signal-regulated kinase 1, Erk1
MAPK7	mitogen-activated protein kinase 7, extracellular signal-regulated kinase 5, Erk5
Mcl-1	induced myeloid leukemia cell differentiation protein
MCP1	monocyte chemoattractant protein 1, chemokine (C-C motif) ligand 2, CCL2
MDA	malondialdehyde, propanedial
MG	methylglyoxal
miRNA	microRNA
miR21	micro RNA-21
MMP-1	matrix metalloproteinase 1
MMP-2	matrix metalloproteinase 2 (gelatinase A)
MMP-7	matrix metalloproteinase 7
MMP-9	matrix metalloproteinase 9 (gelatinase B)
MnSOD	manganese-dependent superoxide dismutase, SOD2
mTOR	mechanistic target of rapamycin
mTORC1	mechanistic target of rapamycin complex 1
N-cadherin	neural cadherin, Cadherin-2
NCCCT	normal cell to cancerous cell transition
Nek7	NIMA-related kinase 7
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
NIH	National Institute of Health
NLRP3	NOD-like receptor family pyrin domain containing 3
NRF2	nuclear factor (erythroid-derived)-like 2, NFE2L2
NSCLC	non-small cell lung cancer
OA	okadaic acid

Osm	oncostatin-M
p27	protein 27, cyclin-dependent kinase inhibitor 1B
p53	protein 53
p70S6K	ribosomal protein S6 kinase beta-1
p107	retinoblastoma-like protein 1, RBL1
p120	catenin delta-1, protein 120
p300	protein 300 (p300-CBP coactivator family)
pAMPK	phosphorylated adenosine monophosphate (AMP) activated protein kinase
PAI-1	plasminogen activator inhibitor-1
PARP	poly-ADP-ribose polymerase
PCK	phosphoenolpyruvate carboxykinase, PEPCK
PCK1	cytoplasmic phosphoenolpyruvate carboxykinase 1, PEPK-C
PCK2	mitochondrial phosphoenolpyruvate carboxykinase 1, PEPK-M
PCN	precancerous niche
PCOS	polycystic ovarian syndrome
pCR	pathological complete response
PD-1	programmed cell death protein 1
PDX	patient-derived xenograft
PELP1	proline-, glutamic acid- and leucine-rich protein-1
PEPCK	phosphoenolpyruvate carboxykinase, PCK
PEPK-C	cytoplasmic phosphoenolpyruvate carboxykinase 1, PCK1
PEPK-M	mitochondrial phosphoenolpyruvate carboxykinase 1, PCK2
PFS	progression free survival
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
PGE2	prostaglandin E2
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
PI3K	phosphatidylinositide 3-kinase
PKA	protein kinase A
PKB	protein kinase B (Akt)
PKM2	pyruvate kinase M2
PP2A	phosphatase protein phosphatase 2A
PPP2R4	serine/threonine-protein phosphatase 2A regulatory subunit B'
Pro-MMP-1	pro-matrix metalloproteinase 1
Pro-MMP-7	pro matrix metalloproteinase 7
Pro-MMP-9	pro-matrix metalloproteinase 9
pS6K1	phosphorylated S6 kinase
PUMA	BH3-only protein
Rac1	Ras-related C3 botulinum toxin substrate 1
RAG	Ragulator-Rag complex
Rap1	Ras-related protein 1, Ras-proximate-1
RAPGEF3	Rap guanine nucleotide exchange factor 3, exchange factor directly activated by cAMP 1, EPAC1
Rho	Ras homolog gene family, member A
RNA	ribonucleic acid
ROS	reactive oxygen species
S1P	sphingosine-1-phosphate
sAC	soluble adenylyl cyclase
sICAM-1	soluble intercellular adhesion molecule-1
Snail	zinc finger protein SNAI1
SOD2	manganese-dependent superoxide dismutase, MnSOD
SOX	[sex-determining region Y (Sry) box-containing] transcription factor family
SOX4	[sex-determining region Y (Sry) box-containing] transcription factor 4
SP1	specificity protein 1
SphK	sphingosine kinase isoform
STAT3	signal transducer and activator of transcriptor 3
STK11	serine/threonine kinase 11, liver kinase B1, LKB1
sVCAM-1	soluble vascular adhesion molecule-1
T2D	type 2 diabetes
TGF-β	transforming growth factor beta
TIMP1	tissue inhibitor of metalloproteinase 1
TNFα	tumor necrosis factor alpha
t-PA	tissue-type plasminogen activator
TSC	tuberous sclerosis complex
TSP-1	thrombospondin-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
VEGF	vascular endothelial growth factor
vWF	von Willebrand factor

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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 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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