Microbiome and morbid obesity increase pathogenic stimulus diversity

Björn L.D.M. Brücher^{1,2,3,*}, Ijaz S. Jamall^{1,2,4}

¹ Theodor-Billroth-Academy®, Germany, USA

² INCORE, International Consortium of Research Excellence of the Theodor-Billroth-Academy®, Germany, USA

³ Department of Surgery, Carl-Thiem-Klinikum, Cottbus, Germany

⁴ Risk-Based Decisions Inc., Sacramento, CA, USA

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Abstract – The microbiome, the relationship between environmental factors, a high-fat diet, morbid obesity, and host response have been associated with cancer, only a small fraction of which (<10%) are genetically triggered. This nongenetic association is underpinned by a worldwide increase in morbid obesity, which is associated with both insulin resistance and chronic inflammation. The connection of the microbiome and morbid obesity is reinforced by an approximate shift of about 47% in the estimated total number of bacteria and an increase from 38,000,000,000,000 in a reference man to 56,000,000,000,000 in morbid obesity leading to a disruption of the microbial ecology within the gut. Humans contain 6,000,000,000 microbes and more than 90% of the cells of the human body are microorganisms. Changes in the microflora of the gut are associated with the polarization of ion channels by butyrate, thereby influencing cell growth. The decrease in the relative proportion of *Bacteroidetes* together with a change in the fermentation of carbohydrates by bacteria is observed in morbid obesity. The disruption of homeostasis of the microflora in the obese changes signaling and crosstalk of several pathways, resulting in inflammation while suppressing apoptosis. The interactions between the microbiome and morbid obesity are important to understand signaling and crosstalk in the context of the progression of the six-step sequence of carcinogenesis. This disruption of homeostasis increases remodeling of the extracellular matrix and fibrosis followed by the none-resolvable precancerous niche as the internal pathogenic stimuli continue. The chronic stress explains why under such circumstances there is a greater proclivity for normal cells to undergo the transition to cancer cells.

Keywords: Cancer, Carcinogenesis, Signaling, Chronic inflammation, Fibrosis, Precancerous niche, Somatic mutation theory, Cell transition, Microbiology, Microbiome, Microflora, Virology, Viriome

Introduction

Microbiology research is changing rapidly, as stated by the American Society of Microbiology (ASM) based on new technologies, globally relevant infectious diseases, and increased resistance to antibiotics [1,2]. Understanding the impact of microbiology on evolution and environment is significant and cultures of microbes may be transformed to the *virtual microbial cell* and we still do not know how artificial intelligence may impact our future understanding of microbiology- and metabolic-driven pathways or their global linkages. Despite the numbers of microbes-driven impact on our understanding of various diseases [3–5], it might not be an understatement that microbiology has driven and still influences life and health [6,7].

Changes in the microflora of the gut are associated with the polarization of ion channels by butyrate, thereby influencing cell growth. The microbiome, the relationship between environmental factors, a high-fat diet, morbid obesity, and host response have been associated with cancer, only a small fraction of which (<10%) are genetically triggered. This nongenetic association is supported by a worldwide increase in morbid obesity, which is associated with both insulin resistance and chronic inflammation. The disruption of homeostasis [8] of the microflora in morbid obesity changes signaling and crosstalk of several pathways, which results in inflammation while suppressing apoptosis.

The interactions between the microbiome and morbid obesity are important to understand signaling and crosstalk in the context of carcinogenesis. This disruption of homeostasis increases remodeling of the extracellular matrix and fibrosis followed by the none-resolvable

*Corresponding author: b-bruecher@gmx.de

Table 1. Microbes in humans and on earth in accordance to references [1,2].

	Microbes	Humans	Factor
On Earth	5×10^{31}	6×10^9	$\sim 10^{22}$
Mass (metric tons)	5×10^{16}	3×10^8	$\sim 10^8$
Generation time	30 min	30 years	$\sim 5 \times 10^5$
Time on Earth/years	3.5×10^9	4×10^5	$\sim 10^4$

precancerous niche (PCN) as the internal pathogenic stimuli with pro-inflammatory mediators ensues [9]. The chronic stress response by the body explains why there is a greater proclivity for normal cells to undergo the transition to cancer cells.

Microbiome (Tab. 1)

The reality in terms of the numbers of microbes on earth with its mass generation time and time on Earth had been provided recently by the American Society of Microbiology (ASM) [1]. Humans did not exist while microbes *collective experience creating and defeating antibiotics for 20 million times longer than Homo sapiens have known that antibiotics existed* [2]. Resistance against antibiotics will occur and any attempt to enhance the immune system will be limited in utility – just a complementary approach as pointed out by Spellberg et al. The numbers provided are amazing as more than 50 quadrillion metric tons microbial cells, 5×10^{31} (50,000,000,000,000,000,000,000,000,000) on earth with much shorter generation times compared to humans (factor $\sim 5 \times 10^{15}$) increase the diversity of life.

Mammalian intestines contain an estimated 10^{10} to 10^{14} microbial cells, which is about 10-fold greater than the number of host cells [3]. The colon has about 10^{14} bacteria [4]. The estimate of the total number of bacteria for a 70 kg individual is about 3.8×10^{13} , which shows that the number of bacteria in the body is on the same order as the number of human cells though the bacterial total mass is estimated to be only about 0.2 kg [5]. This number is approximately equal to the estimated 10^{13} eukaryotic animal cells in an adult human [6].

From the ileum to the cecum there is a bacterial gradient ranging from approximately 10^8 bacteria/g to about 10^{11} bacteria/g as measured in feces [5]. By assuming that red blood cells account for 84% of the total host cells for the reference man, an increase in total bacterial gradient was estimated to occur from an infant of 4 weeks (4.4×10^{12}), a toddler of 1y of age (7×10^{12}), to a 20–30 year reference man of 70 kg (38×10^{12}), a reference woman of 63 kg (44×10^{12}), and an older person of 66 years (38×10^{12}) compared to an obese person of 140 kg with 56×10^{12} [5]. This means an increase of about 47% from 38×10^{12} in a reference man to 56×10^{12} in the morbidly obese. Therefore, it comes as no accident that there is not just a shift of total numbers of microorganisms but also a disruption of the microbial homeostasis within

the gut in morbid obesity associated with a decrease in the relative proportion of *Bacteroidetes* [7].

The numbers provided reveals that de-emphasizing the focus on the host (human body) to a genetic reservoir is not enough. The microbiome with its diversity influences our life and often serves as pathogenic stimuli initiating chronic inflammation [8]. The diversity of the microbiome can result in a dysbiosis triggering a disruption of homeostasis of pro- and anti-inflammatory mediators [9]. Of course, the importance of oral hygiene is well known to be associated with periodontitis, oral plaques, etc. However, affecting the host should not be seen within a localized context as chronic inflammation has much wider effects.

The gram-negative anaerobic *Tannerella forsythia* induces activation of inflammatory cells with increase of interleukin 6 (IL-6), and its bacterial entry is dependent on phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt, PKB), and host Ras-related C3 botulinum toxin substrate 1 (Rac1) guanosine-5'-triphosphate (GTP)ase, and its endocytosis, which needs lipid microdomains and clathrin [10].

T. forsythia expresses two sialidases, SiaHI and NanH, which are important in bacterial colonization [11]. Oral microbiome composition alters fatty acid metabolism [12] and are not just associated with oral cancer development [13] but also are suspected of promoting esophageal [14,15], pancreatic cancer [16,17], or liver cancer [18]. *T. forsythia* “contributes to the growth of a partner species, *Fusobacterium nucleatum*, in co-biofilms” [19]. *F. nucleatum* is associated with the precancerous serrated adenoma of the proximal colon [20] and various cancers [21,22].

We assert that the renaissance in microbiology for cancer research has commenced and that it needs an increased effort with close interdisciplinary impact and collaboration between various disciplines.

The Human Microbiome Project (HMP) showed that there is no single healthy microbiome [23] and that there might also be no unhealthy microbiome. The gut microbiome is associated with metabolic signaling pathways such as tumor necrosis factor alpha (TNF α) and interferon gamma (IFN γ) through palmitoleic acid and tryptophan metabolism [24]. The palmitoleic acid metabolism was associated with cancer as “...significantly lower content of palmitoleic acid compared to their counterpart non-stem cancer cells” were shown [25].

An explanation was suggested by the demonstration that distant bioelectric signaling suppressed cancer growth by misexpression of hyperpolarizing ion channels and that this effect was mediated by the short-chain fatty acid, butyrate, which is usually produced in the colonic mucosa through bacterial fermentation of carbohydrates [26]. If these findings are reproducible, one plausible way to prevent cancer might be to re-program gut microorganisms to produce butyrate. However, there is evidence that different single components of the microbiome may trigger carcinogenesis through the recently proposed six-step sequence which includes pathogenic biological

stimuli that provoke subclinical chronic inflammation leading to fibrosis with remodeling of the extracellular matrix (ECM) resulting into a precancerous niche (PCN) [27].

Proteomic analysis can help to identify biological processes that could be of importance in carcinogenesis [28]. *Schistosoma haematobium* was associated with bladder cancer using proteomic profiling [29]. Products of the nematode, *Anisakis pegreffii*, were shown to upregulate heat shock protein 70 (Hsp70) with a corresponding decrease in apoptosis [30].

There is also an attempt to use RNA profiling data using differential expression to assess if these data “are sufficient to make the normal and redirected gene expression states indistinguishable from each other but radically different from the tumor state” [31].

It has been proposed that multitargeted cancer therapy against multiple markers could be of future benefit [32]. However, such an approach using RNA would need to differentiate between the different types of RNA. For example, transfer RNAs (tRNAs; synonym: soluble RNA, sRNA) help decode messenger RNA (mRNA) to form a protein and each codon represents a particular amino acid that is recognized by a specific tRNA. tRNA carries an amino acid to the ribosome (directed by a three-nucleotide-sequence in a mRNA) and one tRNA end matches the genetic code (called an anticodon). The involvement of tRNA pathways in cell proliferation and tumorigenesis was recently shown by analyzing breast and prostate cancer cell lines [33]. Furthermore, some 80% of RNAs are short-lived and exist for *less than 2 min* [34]. This is relevant as protocols used to investigate RNA would have to stipulate the stability of the RNA used, and if stored or frozen, RNA pellets were reconstituted after fluids and/or tissue samples were collected and thus provide information about the quality of material used.

Western diets (typically high in animal protein, sugar, starch, fat, and low in fiber) can trigger chronic systemic inflammation [35] and influence the composition of the intestinal microbiota [36]. The composition of the microbiome in humans is associated with cancer. A greater gut bacterial diversity was tied to slower metastatic melanoma progression, while the patient group with higher bacterial diversity had not reached the median progression free survival (PFS) (more than half had not even progressed), whereas those with intermediate and low bacterial diversity had median PFS of 232 and 188 days, respectively [37]. Patients responding to immunotherapy showed increased levels of Ruminococcaceae, while non-responding patients showed enriched Bacteroidales. This was interpreted as relevant since patients who had a high abundance of the genus *Faecalibacterium* (of the Ruminococcaceae family and Clostridiales order) in their gut exhibited significantly prolonged PFS (median not reached) as compared to patients who had a low abundance (median PFS of 242 days). Moreover, the greater abundance of Bacteroidales was associated with more rapid disease progression in melanoma, with high abundance within the gut microbiome associated with

significantly reduced PFS (median 188 days) compared to low abundance (median PFS of 393 days). Additionally, immunotherapy responders showed high levels of the beneficial *Clostridiales/Ruminococcaceae*, including greater T cell penetration into tumors and higher levels of circulating T cells that kill abnormal cells. Those with abundant Bacteroidales had higher levels of circulating regulatory T cells, myeloid-derived suppressor cells, and a blunted cytokine response resulting in a dampening of antitumor immunity.

Pattern recognition receptors (PRRs) include the membrane-bound Toll-like receptors (TLRs) and C-type lectins (CTLs) and are expressed in macrophages, monocytes, neutrophils, epithelial cells and cells of the innate immune system that stimulate inflammation [38]. Receptors recognizing pathogens contain NOD-like receptors (NLRs) and were reported as a novel class of PRRs. NLRs are sensors of pathogen-associated molecular patterns (PAMPs) and host-derived danger signals; danger-associated molecular patterns (DAMPs) lead to an inflammatory response (reviewed in [39–41]). NLRs contain a NOD-, leucine-rich repeat (LRR) NLR and pyrin domain-containing 1 and include NACHT, LRR and PYD domain-containing protein 3 (NLRP3, NALP3), NLR family CARD domain-containing protein 4 (NLRC4), NACHT, LRR, and PYD domain-containing protein 6 (NLRP6), NACHT, LRR and PYD domain-containing protein 7 (NLRP7), NACHT, LRR and PYD domain-containing protein 12 (NLRP12) or NLRC4 [42].

In encephalomyelitis NLRP12 negatively regulates the nuclear factor-kappa B (NF- κ B) pathway suppressing inflammation [43].

In NLRP12-deficient mice, NF- κ B activation is increased in association with colitis-associated colon cancer [44], which is in accordance with low-expressed NLRP12 in precancerous ulcerative colitis [45]. Human adipose tissues of obese patients have decreased NLRP12 levels and knockout results in weight gain and chronic inflammation [46]. NLRP12 maintained colon microbiome diversity, attenuated colon inflammation, and promoted specific microbes that reversed gut inflammation [45]. Thus, NLRP obesity protection is dependent on the microbiome [46]. NLRP12 was reported as a regulator of homeostasis for inflammation and NF- κ B signaling pathway and crosstalk [47], but the microbiome data reviewed [45,46] may provide evidence about the important influence of the microbiome with dysbiosis on chronic inflammation, obesity, and the consequent disruption of homeostasis.

Colonic microbiota investigated together with host response genes in fecal and mucosal samples from colorectal cancer (CRC) patients compared to patients with polyps and healthy controls revealed microbiota composition in regard to localization of the primary tumor [48]. The authors stratified the patients in accordance with tissue-associated microbial co-abundance Groups (CAGs). Concerns were raised in terms of microbiota based on cancer site due to the wide variability in the microbiota data [49] and the authors reanalyzed their data in accordance to CAGs and reported that two CAGs at

surgery were associated with longer survival in CRC together with an association of “pre-surgery faecal microbiota with stability of the microbiota after surgery” [50]. The same group investigated microbiota in oral swabs and compared it to results from colonic mucosae and stool probes in CRC and stated that “high abundance of Lachnospiraceae was negatively associated with the colonisation of colonic tissue with oral-like bacterial networks suggesting a protective role for certain microbiota types against CRC, possibly by conferring colonisation resistance to CRC-associated oral taxa and possibly mediated through habitual diet” [51]. However, investigating microbiota is not enough [52] as dynamic changes need to be considered [53].

However, the approach of the disruption of signaling homeostasis-induced crosstalk in the carcinogenesis paradigm “Epistemology of the origin of cancer” is strongly supported by the evidence provided within the various publications of this Special Issue and in terms of the microbiome as dysbiosis with changes in inflammation together with cancer development along the adenoma-carcinoma sequence has been provided [54] without any mutation.

The microbiome is studied in an effort to understand morbid obesity as a metabolic condition beyond just caloric intake [55]. In this context, it has been shown that microbial flora from the cecum of obese mice when introduced into germ-free mice resulted in increased obesity even with lower food consumption while the reverse, introducing bacterial flora from lean mice, resulted in weight loss [56]. Furthermore, it has also been shown that a relationship exists between environmental factors and the host insofar as a high-fat diet appears to promote intestinal cancers leading to the hypothesis that antibiotics might block or otherwise mitigate such cancers. More recently, it was shown that the changes in the composition of the intestinal flora (=dysbiosis) may be causally responsible for this observed increase in intestinal cancer incidence [57]. In all likelihood, chronic inflammation induced by morbid obesity could lead to fibrosis with consequent remodeling of the ECM, which in turn, facilitates the transition of a normal cell to a cancer cell.

Morbid obesity

Morbid obesity is associated with various diseases which, in turn, are themselves associated with chronic inflammation such as is known for cardiovascular diseases, noninsulin-dependent diabetes mellitus (NIDDM), osteoarthritis, and cancer [55]. Lack of physical activity combined with excessive caloric intake along with other factors such as socioeconomic variables, as well as psychiatric and/or metabolic diseases are some of the explanations given for the rise of morbid obesity [58]. Genetics can explain an estimated 7% of obesity [59].

The body mass index (BMI) does not allow one to distinguish lean body mass from fat body mass. Patients with coronary artery diseases or heart failure over 65 years of age with moderate obesity (BMI = 30–35) compared to

normal weight people (BMI = 20–25) and morbidly obese (BMI > 35) revealed a decrease in mortality [60]. This paradox was published first in 1999 ([61], reviewed in [62]) and has so far not been satisfactorily explained.

Morbid obesity can be viewed as an internal pathogenic stimulus triggering carcinogenesis because of its association with subclinical inflammation in adipose tissue [63–66] even though its precise role is not fully understood. Diagnostic upper gastrointestinal endoscopies in morbidly obese patients revealed that some 80% exhibit pathologic findings in spite of the fact that most such patients are asymptomatic [67].

Obesity has been strongly associated with precancerous lesions and conditions such as colon adenomas [68–86], monoclonal gammopathy [87–98], chronic pancreatitis [99–102], or inflammatory bowel disease (IBD) [103–106]. Observed risks of cancers associated with obesity include breast [107–111], colorectal [112–115], pancreatic [99–102,116], endometrial [117], prostate [118], renal cell carcinoma [119], and lymphoma or leukemia [87–98,120]. Furthermore, obesity is linked to multiple cancers and a nationwide study in Germany suggested preventive potential in these obesity-associated cancers [121].

The paradox that obesity was also reported with nonsignificant associations of obesity and patient outcomes in lymphoma [122] or with improved survival in lymphoma [123–125] is not well understood. Otherwise, bariatric surgery with induced weight loss resulted in regression of hepatocellular carcinoma (HCC) [126], highlighting the significance of morbid obesity with chronic inflammation in carcinogenesis.

Obesity increases resistance against anti-vascular endothelial growth factor (VEGF) drugs due to the ongoing pro-inflammatory cytokine IL-6 and the pro-fibrotic mediator fibroblast growth factor 2 (FGF-2) which result in decreased sensitivity against anti-VEGF therapy [127]. We contend that the ongoing chronic inflammation continuously promotes the creation of the PCN. Furthermore, it should be noted that metformin inhibited FGF-2 in the experiments (Figs. 7a and 7b of Ref. [127] not shown here). ECM remodeling activated by obesity with its underlying chronic inflammation suggests that obesity or chronic inflammation is not enough as it needs fibrosis, which is subsequently remodeled for aggressive cancer phenotype cells that show enhanced growth and invasiveness [128].

One plausible explanation might be to examine how chronic inflammation induced by morbid obesity explains its association with carcinogenesis as has been previously suggested to examine how nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling plays a crucial in carcinogenesis [27], and how inhibition of the pro-inflammatory inhibitor of kappa B kinase beta (IKK β)/NF- κ B signaling has been shown to be a central pathway in regard to high-fat diet-induced obesity and glucose intolerance [129]. Exogenous fat-induced insulin resistance develops by endogenous fatty acid synthesis in macrophages through modulation of the plasma membrane and through chronic inflammation [130].

Inflammation in adipose tissue (Fig. 1) occurs with early-onset insulin resistance by phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma isoform (PI3K γ) activity in leukocytes; PI3K γ affects macrophage gene expression by non-cell autonomous mechanisms, e.g., autocrine cytokines [131]. Inflammation in obesity is activated by G-protein coupled receptor family C group 5 member B (GPRC5B) in adipocytes linking GPRC5B diet-induced obesity to type 2 diabetes (T2D) [132]. Morbid obesity-induced inflammation facilitates cancer progression by neutrophils that are recruited by adipocyte-secreted interleukin beta 1 (IL- β 1) resulting in chronic inflammation, which, if persistent, can result in fibrosis and the development of the PCN [133].

The cytokine chemokine (C-X-C motif) ligand 1 (CXCL1) (synonyms: melanoma growth-stimulating activity alpha, GRO1, GRO α ; neutrophil-activating protein 3 (NAP3), fibroblast secretory protein (FSP)), is released by macrophages, neutrophils, and the epithelium. CXCL1 binds neutrophils at sites of inflammation, is activated by RAS [134], and is reported to be a mitogen [135].

T2D is associated with β cell stress and chronic inflammation as well as subclinical pancreatitis, which increases CXCL1 and triggers proliferation in the human pancreatic ductal epithelium [136]. Interleukin 17 (IL-17) induces the expression of regenerating islet-derived protein 3-beta (REG3 β), which is a mediator of pancreatitis during acinar-to-ductal metaplasia and in early pancreatic intraepithelial neoplasia (PanIN) lesions. The REG3 β glycoprotein130 (gp130)/Janus kinase 2 (JAK2)/signal transducers and activators of transcription (STAT3)-dependent pathway decreases sensitivity to cell death, thereby promoting cell growth. The genetic inactivation of REG3 β in the context of Kras-driven pancreatic ductal adenocarcinoma (PDAC) resulted in reduced PanIN formation, an effect that could be rescued by the administration of exogenous REG3 β [137].

Plasminogen activator inhibitor-1 (PAI1) is produced in the endothelium of blood vessels and in adipocytes and is increased in obesity as well as in cancers. Interestingly, PAI1 promotes fibrosis (Fig. 1) by the pathologic disruption of connective tissue and is increased by Angiotensin II and associated with another chronic disease, atherosclerosis.

ORM1 (synonyms: α 1-acid glycoprotein, orosomucoid, α 1Agp, AGP, AAG) is synthesized in hepatocytes as an acute phase protein and stabilized by interaction with the PAI1 inhibitory activity [138]. Thus, morbid obesity is associated with an increase of PAI1 by adipocytes, is an inhibitor of fibrinolysis (Fig. 1), and can promote fibrosis, which is also increased by Angiotensin II. These factors may serve to explain why morbid obesity is associated with fibrosis [139]. Furthermore, adipocytes can affect a continuous increase of PI3K and chronic PI3K as well as transforming growth factor beta 1 (TGF- β 1) and these, in concert, result in Akt-mediated SNAIL-stabilization [140] necessary for generating metalloproteinase 1 (MMP-1) and metalloproteinase 7 (MMP-7). There is also a decrease

of the forkhead box protein O3a (FOXO3a) associated with increases of Bcl-2-like protein 11 (Bim) and p53 upregulated modulator of apoptosis (PUMA), inhibiting apoptosis [141]. Consequently, anti-apoptotic proteins such as caspase-8 inhibitor and CASP8 and Fas-associated protein with death domain (FADD)-like apoptosis regulator (FLIP) are upregulated [142], which result in lowered internal protection against oxidative stress.

The gene for leptin was discovered by Friedmann and coworkers in 1994 [143]. Leptin is produced by adipocytes and promotes the synthesis of α -melanocyte-stimulating hormone (α -MSH) within the medial hypothalamus resulting in the inhibition of hunger. It further counteracts the hunger promotor, 36-amino acid neuropeptide (neuropeptide Y, NPY), within the lateral hypothalamus [144–146], which is released in the gut and the hypothalamus and *N*-arachidonylethanolamine (anandamide, AEA) [147] and is synthesized by *N*-arachidonoyl phosphatidylethanolamine (NAPE) through an *N*-acyltransferase enzyme stimulating satiety [148].

Physiological levels of leptin result in selective suppression of TNF α in macrophage subpopulations by food withdrawal as a centrally mediated anti-inflammatory effect, which is incompletely understood [149].

Paradoxically, leptin has an anti-hunger effect, yet increased levels are found in morbid obesity compared to normal-weight individuals [150], an observation of leptin resistance akin to insulin resistance seen in diabetics. Leptin is similar to the inflammatory cytokine, IL-6 [151], and has an inflammatory [152] and pro-carcinogenic effect via the Janus kinase/signal transducers and activators of transcription (Jak/STAT3) pathway, PI3K/Akt pathway, through up-regulating cyclin-dependent kinase 2 (cdk2, cell division protein kinase 2) and cyclin D1, activating the mitogen-activated protein kinase (MAPK) pathway (through extracellular signal-regulated kinase 1 (Erk1) and extracellular signal-regulated kinase 2 (Erk2) phosphorylation) and also by stimulating the STAT3 pathway and up-regulation of *c-myc* (one target gene of STAT3) ([153], reviewed in [154]).

Leptin results in a six-fold *reduction* of apoptosis, an increase in angiogenesis [155], and increases in cultured cytotrophoblastic cells in a dose-dependent manner with metalloproteinase 2 (MMP-2), and fetal fibronectin (fFN), which itself promotes and elevates metalloproteinase 9 (MMP-9) activity ([156,157], reviewed in [155]).

Apoptosis is reduced through stimulation of NF- κ B signaling ([158], reviewed in [155]). Apoptosis is inhibited by leptin in chondrocytes through upregulation of lysyl oxidase-like 3 (LOXL3) mRNA expression via activation of mammalian target of rapamycin complex 1 (mTORC1) [159] (Fig. 1), while the lysyl oxidase inhibitor, β -aminopropionitrile (BAPN), reduces leptin's pro-fibrotic effects and ameliorates cardiovascular remodeling in diet-induced obesity in rats [160]. Otherwise, leptin-replacement therapy results in cancer-related adverse effects [161].

Fig. 1. Simplified scheme of the disruption of signaling homeostasis-induced crosstalk in the carcinogenesis paradigm “Epistemology of the origin of cancer” focusing on energy homeostasis and morbid obesity. The scheme consists 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. 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- κ B signaling and crosstalk during carcinogenesis”. *Nomenclature:* The nomenclature common abbreviations are in 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; **TNF α** tumor necrosis factor alpha; **IFN γ** interferon gamma; **ALOX** lipoxygenase, arachidonate lipoxygenase; **ALOX12** 12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type; **ALOX5** 5-lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase; **12-HETE** 12-hydroxyeicosatetraenoic acid; **LTA4** leukotriene A4, 4-[(2S,3S)-3-[(1E,3E,5Z,8Z)-tetradeca-1,3,5,8-tetraenyl]oxiran-2-yl]butanoic acid; **LTB4** leukotriene B4, (5S,6Z,8E,10E,12R,14Z)-5,12-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-EETE** (6E, 8Z,11Z,14Z)-5-oxoicosa-6,8,11,14-tetraenoic acid; **Cox** cyclooxygenase; **Cox-1** cyclooxygenase 1; **Cox-2** cyclooxygenase 2; **Cox-3** isoform of Cox-2 (therefore in brackets); **PGG2** prostaglandin G2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroperoxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; **PGH2** prostaglandin H2, (Z)-7-[(1S,4R,5R,6R)-5-[(E,3S)-3-hydroxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid; **PGFF2 α** 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- β 1** interleukin beta 1; **IL-33** interleukin 33; **ROS** reactive oxygen species; **CXC** CC chemokine receptors; **α SMAD** alpha-smooth muscle actin; **miR21**

The lipogenic enzyme, acetyl-CoA carboxylase 1 (ACC1), has a central function in fatty acid synthesis [162,163]. Inhibition of ACC1 occurs by phosphorylation induced by leptin and mediated through transforming growth factor beta (TGF- β) signaling by activating TGF- β -activated kinase 1 (TAK1). This enzymatic reaction results in the elevation of Smad2 transcription factor acetylation and activation, resulting in cell transition and metastases in mice. Inactive ACC1 levels were found to be increased in metastatic human breast cancer while inhibiting leptin reduced metastasis [164]. This is in accordance with the finding that leptin itself triggers metastasis in A549 lung cancer cells in vitro [165]. As leptin and TGF are increased in obese individuals [166–169], ACC1 can be inactivated during chronic inflammation.

It has recently been shown that lysyl oxidase is increased in morbidly obese patients [170]. This results in an ongoing stimulation of multiple pathways illustrated in Fig. 1. It is known that there is a negative leptin/TGF- β signaling loop [170,171], but leptin was shown to augment signaling in lung fibroblasts by inhibiting the inhibitor of the transcriptional response to TGF- β 1 via inhibition of peroxisome proliferator-activated receptor- γ (PPAR γ) [172]. This again shows that here also disruption of homeostasis plays a key early role in carcinogenesis. Furthermore, leptin induces cell proliferation and inhibits apoptosis in human hepatocellular carcinoma (HCC) via promotion of Cyclin D1 and Bax/Janus-kinase-2 signaling [173].

The influence of the composition of the microbiome in cancer patients shows that it influences cancer progression and may well play a role in cancer therapy as is illustrated by the metastatic melanoma data [37]. An increased gut bacterial diversity was associated with decreased progression and improved progression-free survival (PFS). Patients with enriched *Ruminococcaceae* family were associated with responders to immunotherapy, while nonresponders showed a higher composition with *Bacteroidales*. Abundance of *Faecalibacterium* revealed prolonged PFS, while *Bacteroidales* abundance was associated with more rapid disease progression and decreased PFS. Furthermore, enriched *Ruminococcaceae* family showed higher levels of circulating T cells, while

Bacteroidales abundance showed lower circulating regulatory T cells, myeloid derived suppressor cells, and a blunted cytokine response.

Inoculating commercial broiler chickens with infectious bursal disease high virulent strain *vvIBDV strain 89163/7.3* resulted into a change of the gut microbiome composition with abundance of *Clostridium XIVa* and *Faecalibacterium* compared to virus-free birds indicating an impact to gut-associated lymphoid tissues [174]. Therefore, it was suggested that after the acute phase, gut-associated lymphoid tissue could be modulated by dysregulation of gut mucosal immunity. CRC [175] and IBD [176] are associated with abundance of *Faecalibacterium prausnitzii* (reviewed in [174]). These findings may impact future virus infection research and its influence on reservoir species, as well as on microbiome and chronic inflammation.

Summary

The microbial ecology has huge impact on life, evolution, as well as pathogenic stimuli on the development on cancer. The interplay of pathogenic stimuli with consequent chronic inflammation [8,9], proteins [177], and the release of cytokines from many cell types provide a micromilieu promoting the PCN (Fig. 1). The complexity of dysregulated homeostasis increases when one considers the microbiome, high-fat diet, and morbid obesity [178]. The microbial flora itself can increase obesity. The effects of changes in the composition of such symbionts in humans on signaling pathways and induced crosstalk are appreciable and influence metabolism and signaling pathways in various ways triggering chronic inflammation, cell proliferation, and the inhibition of apoptosis. Even pathogenic viral stimuli influence gut-associated lymphoid tissue to modulate the microbiome composition. Pathogenic stimuli, with its consequent chronic inflammation, and the interplay of ubiquitous proteins, corresponding enzymes, and eicosanoids are influenced by the microbiome and morbid obesity resulting in the “Disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm Epistemology of the origin of cancer.” Remodeled fibrosis results in another prerequisite for the development of cancer (carcinogenesis) – the PCN.

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

Nomenclature

5-oxo-ETE	(6 <i>E</i> ,8 <i>Z</i> ,11 <i>Z</i> ,14 <i>Z</i>)-5-oxoicosa-6,8,11,14-tetraenoic acid	FOXO3a	forkhead box protein O3a
12-HETE	12-hydroxyeicosatetraenoic acid	FSP	fibroblast secretory protein
20-HETE	20-hydroxyeicosatetraenoic acid, (5 <i>Z</i> ,8 <i>Z</i> ,11 <i>Z</i> ,14 <i>Z</i>)-20-hydroxyicosa-5,8,11,14-tetraenoic acid	Hsp70	heat shock protein 70
20-OH-PGE2	20-hydroxy prostaglandin E2	gp130	glycoprotein 130
α-MSH	alpha melanocyte-stimulating hormone	GPRC5B	G protein-coupled receptor family C group 5 member B
αSMAD	alpha-smooth muscle actin	GROα	melanoma growth stimulating activity alpha, CXCL1, GRO1, MSGA-α, NAP3
ACC1	acetyl-CoA carboxylase 1	GRO1	melanoma growth stimulating activity 1, melanoma growth stimulating activity alpha, GROα, CXCL1, MSGA-α, NAP3
AEY	<i>N</i> -arachidonoyl ethanolamine (anandamide)	GTP	guanosine-5'-triphosphate
Akt	protein kinase B (=PKB)	HCC	hepatocellular carcinoma
ALOX	lipoxygenase, arachidonate lipoxygenase	HMP	Human Microbiome Project
ALOX12	12-lipoxygenase, 12-LOX, 12S-LOX, arachidonate 12-lipoxygenase 12S type; activator protein 1	IBD	inflammatory bowel disease
AP1	activator protein 1	IFNγ	interferon gamma
ASM	American Society of Microbiology	IKKβ	inhibitor of kappa B kinase beta
BAPN	β-aminopropionitrile	IL-β1	interleukin beta 1
BIM	Bcl-2 interacting mediator of cell death	IL-6	interleukin 6
BMI	body mass index	IL-8	interleukin 8
CAG	co-abundance group	IL-17	interleukin 17
cdc42	cell division control protein 42 homolog	IL-33	interleukin 33
cdk2	cyclin-dependent kinase 2	JAK2	Janus kinase 2
Cox	cyclooxygenase	MMP-1	metalloproteinase 1
Cox-1	cyclooxygenase 1	MMP-2	metalloproteinase 2
Cox-2	cyclooxygenase 2	MMP-7	metalloproteinase 7
Cox-3	isoform of Cox-2 (therefore in brakes)	MMP-9	metalloproteinase 9
CRC	colorectal cancer	LOX5	5-lipoxygenase, 5-LOX, arachidonate 5-lipoxygenase
CSES	chronic stress escape strategy	LOXL3	lysyl oxidase homolog 3
CTL	C-type lectin	LRR	leucine rich repeat
CYP*	cytochrome P450 isoforms	LTA4	leukotriene A4, 4-[(2 <i>S</i> ,3 <i>S</i>)-3-[(1 <i>E</i> ,3 <i>E</i> ,5 <i>Z</i> ,8 <i>Z</i>)-tetradeca-1,3,5,8-tetraenyl]oxiran-2-yl]butanoic acid
CXC CC	chemokine receptors	LTB4	leukotriene B4, (5 <i>S</i> ,6 <i>Z</i> ,8 <i>E</i> ,10 <i>E</i> ,12 <i>R</i> ,14 <i>Z</i>)-5,12-dihydroxyicosa-6,8,10,14-tetraenoic acid
CXCL1	chemokine (C-X-C motif) ligand 1, GROα, GRO1, MSGA-α, NAP3	LTC4	leukotriene C4, (5 <i>S</i> ,6 <i>R</i> ,7 <i>E</i> ,9 <i>E</i> ,11 <i>Z</i> ,14 <i>Z</i>)-6-[(2 <i>R</i>)-2-[(4 <i>S</i>)-4-amino-4-carboxybutanoyl]amino]-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid
C-X-C	cytokine chemokine (C-X-C motif)	LTD4	leukotriene D4, (5 <i>S</i> ,6 <i>R</i> ,7 <i>E</i> ,9 <i>E</i> ,11 <i>Z</i> ,14 <i>Z</i>)-6-[(2 <i>R</i>)-2-amino-3-(carboxymethylamino)-3-oxopropyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid
CXCR4	C-X-C motif of chemokine receptor 4	LTE4	leukotriene E4, (5 <i>S</i> ,6 <i>R</i> ,7 <i>E</i> ,9 <i>E</i> ,11 <i>Z</i> ,14 <i>Z</i>)-6-[(2 <i>R</i>)-2-amino-2-carboxyethyl]sulfanyl-5-hydroxyicosa-7,9,11,14-tetraenoic acid
DAMP	danger associated molecular patterns	MAPK	mitogen-activated protein kinase
E2F4/5	cytoplasmic complex of Smad3, retinoblastoma-like protein 1 (P107, RBL1), E2F4/5 and d-prostanoid (DP1)	MAPK3	mitogen-activated protein kinase 3, extracellular signal-regulated kinase 1, Erk1
E-Cadherin	CAM 120/80 or epithelial cadherin, cadherin-1, epithelial cadherin	MAPK7	mitogen-activated protein kinase 7, extracellular signal-regulated kinase 5, Erk5
ECM	extracellular matrix	MDA	malondialdehyde, propanedial
Erk1	extracellular signal-regulated kinase 1, mitogen-activated protein kinase 3, MAPK3	miR21	micro RNA-21
Erk2	extracellular signal-regulated kinase 2, mitogen-activated protein kinase 1, MAPK1	MMP-1	matrix metalloproteinase 1
FADD	Fas-associated protein with death domain	MMP-2	matrix metalloproteinase 2
fFN	fetal fibronectin		
FGF-2	fibroblast growth factor-2		
FLIP	CASP8 and Fas-associated protein with death domain (FADD)-like apoptosis regulator		

MMP-7	matrix metalloproteinase 7	PI3K γ	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma isoform
mRNA	messenger RNA	PPAR γ	peroxisome proliferator-activated receptor- γ
MSGA- α	melanoma growth stimulating activity, alpha, CXCL1, GRO α , GRO1	Pro-MMP-1	pro-matrix metalloproteinase 1
mTORC1	mammalian target of rapamycin complex 1 or mechanistic target of rapamycin complex 1	Pro-MMP-7	pro matrix metalloproteinase 7
NAP3	neutrophil-activating protein 3, CXCL1, GRO1, GRO α , MSGA- α	Pro-MMP-9	pro-matrix metalloproteinase 9
NAPE	<i>N</i> -arachidonoyl phosphatidylethanolamine	PRR	pattern recognition receptors
NCCCT	normal cell to cancerous cell transition	PUMA	BH3-only protein
NF- κ B	nuclear factor kappa-light-chain-enhancer of activated B cells	Ras	Ras-subfamily: family of related proteins
NIDDM	diabetes mellitus type 2	Rac1	Ras-related C3 botulinum toxin substrate 1
NLR	NOD-like receptor	REG3 β	regenerating islet-derived protein 3-beta
NLRC4	NLR family CARD domain-containing protein 4	Rho	Ras homolog gene family, member A
NLRP3	NACHT, LRR and PYD domains-containing protein 3	ROS	reactive oxygen species
NLRP6	NACHT, LRR and PYD domains-containing protein 6	S1P	sphingosine-1-phosphate
NLRP7	NACHT, LRR and PYD domains-containing protein 7	SNAIL	zinc finger protein SNAI1
NLRP12	NACHT, LRR and PYD domains-containing protein 12	SOX	[sex-determining region Y (Sry) box-containing] transcription factor family
NPY	neuropeptide Y	SP1	specificity protein 1
ORM1	α 1-Acid glycoprotein, orosomucoid, α 1Agp, AGP, AAG	SphK	sphingosine kinase isoform
Osm	oncostatin-M	sRNA	soluble RNA, tRNA
p107	retinoblastoma-like protein 1, RBL1	STAT3	signal transducers and activators of transcription
p120	catenin delta-1, protein 120	T2D	type 2 diabetes
p300	protein 300 (p300-CBP coactivator family)	TAK1	transforming growth factor beta-activated kinase 1
PAI1	plasminogen activator inhibitor-1	TGF- β 1	transforming growth factor beta 1
PanIN	pancreatic intraepithelial neoplasia	TLR	Toll-like receptor
PAMP	pathogen-associated molecular pattern	TNF α	tumor necrosis factor alpha
PDAC	pancreatic ductal adenocarcinoma	tRNAs	transfer RNAs, sRNA
PKB	protein kinase B (=AKT)	TXA2	thromboxane A2, (<i>Z</i>)-7-[(1 <i>S</i> ,2 <i>S</i> ,3 <i>R</i> ,5 <i>S</i>)-3-[(<i>E</i> ,3 <i>S</i>)-3-hydroxyoct-1-enyl]-4,6-dioxabicyclo[3.1.1]heptan-2-yl]hept-5-enoic acid
PCN	precancerous niche	VEGF	vascular endothelial growth factor
PGG2	prostaglandin G2, (<i>Z</i>)-7-[(1 <i>S</i> ,4 <i>R</i> ,5 <i>R</i> ,6 <i>R</i>)-5-[(<i>E</i> ,3 <i>S</i>)-3-hydroperoxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid		
PGH2	prostaglandin H2, (<i>Z</i>)-7-[(1 <i>S</i> ,4 <i>R</i> ,5 <i>R</i> ,6 <i>R</i>)-5-[(<i>E</i> ,3 <i>S</i>)-3-hydroxyoct-1-enyl]-2,3-dioxabicyclo[2.2.1]heptan-6-yl]hept-5-enoic acid		
PGFF2 α	prostaglandine F2 alpha, (<i>Z</i>)-7-[(1 <i>R</i> ,2 <i>R</i> ,3 <i>R</i> ,5 <i>S</i>)-3,5-dihydroxy-2-[(<i>E</i> ,3 <i>S</i>)-3-hydroxyoct-1-enyl]cyclopentyl]hept-5-enoic acid		
PGD2	prostaglandin D2, (<i>Z</i>)-7-[(1 <i>R</i> ,2 <i>R</i> ,5 <i>S</i>)-5-hydroxy-2-[(<i>E</i> ,3 <i>S</i>)-3-hydroxyoct-1-enyl]-3-oxocyclopentyl]hept-5-enoic acid		
PGE2	prostaglandin E2, (<i>Z</i>)-7-[(1 <i>R</i> ,2 <i>R</i> ,3 <i>R</i>)-3-hydroxy-2-[(<i>E</i> ,3 <i>S</i>)-3-hydroxyoct-1-enyl]-5-oxocyclopentyl]hept-5-enoic acid		
PI3K	phosphatidylinositide 3-kinase		

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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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