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Review

Somatic Mutation Theory - Why it's Wrong for Most Cancers

Björn L.D.M. Brücher[a-d] Ijaz S. Jamall[a,b,e]

[a]Theodor-Billroth-Academy®, Munich, Germany – Sacramento, California, USA; [b]INCORE, International Consortium of Research Excellence of the Theodor-Billroth-Academy®, Munich, Germany – Sacramento, California, USA; [c]Bon Secours Cancer Institute, Richmond, VA, USA; [d]Dep. Of Surgery, Carl-Thiem-Klinikum, Cottbus, Germany; [e]Risk-Based Decisions Inc., Sacramento, CA, USA

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Carcinogenesis • Somatic mutation theory • Microenvironment • Cell communication • Signaling • Inflammation • Chronic inflammation • Fibrosis • Cell transition • Precancerous niche

Abstract
Hysteron proteron reverses both temporal and logical order and this syllogism occurs in carcinogenesis and the somatic mutation theory (SMT): the first (somatic mutation) occurs only after the second (onset of cancer) and, therefore, observed somatic mutations in most cancers appear well after the early cues of carcinogenesis are in place. It is no accident that mutations are increasingly being questioned as *the* causal event in the origin of the vast majority of cancers as clinical data show little support for this theory when compared against the metrics of patient outcomes. Ever since the discovery of the double helical structure of DNA, virtually all chronic diseases came to be viewed as causally linked to one degree or another to mutations, even though we now know that genes are not simply blueprints, but rather an assemblage of alphabets that can, under non-genetic influences, be used to assemble a business letter or a work of Shakespearean literature. A minority of all cancers is indeed caused by mutations but the SMT has been applied to all cancers, and even to chemical carcinogenesis, in the absence of hard evidence of causality. Herein, we review the 100 year story of SMT and aspects that show why genes are not just blueprints, how radiation and mutation are associated in a more nuanced view, the proposed risk of cancer and bad luck, and the *in vitro* and *in vivo* evidence for a new cancer paradigm. This paradigm is scientifically applicable for the majority of non-heritable cancers and consists of a six-step sequence for the origin of cancer. This new cancer paradigm proclaims that somatic mutations are epiphenomena or later events occurring after carcinogenesis is already underway. This serves not just as a plausible alternative to SMT and explains the origin of the majority of cancers, but also provides opportunities for early interventions and prevention of the onset of cancer as a disease.

Björn LDM Brücher, MD, PhD,
FRCS (Engl.), FACS, Professor of Surgery

Department of Surgery, Carl-Thiem-Klinikum, Cottbus, (Germany)
Tel. +49-(0)355-46-2337, E-Mail b-bruecher @gmx.de

Introduction

The hysteron proteron of the somatic mutation theory (SMT) appears because the first event (mutations), in fact occur later in the process, i.e., only after the cell has been transformed from a normal cell to a cancer cell via a process termed carcinogenesis. Mutations have increasingly been perceived as *the* causal event in the origin of the vast majority of cancers even as clinical data show little support for this theory when compared against the metrics of patient outcomes. Another challenge is the lack of reproducibility [1] as less than 20% of so-called highly ranked 'landmark' papers have been irreproducible [2]. Despite methodological issues, this seems to be a multifactorial omission insofar as original references are increasingly not read and/or cited with a lack of critical analysis resulting in the dominance of erroneous conclusions from research data [3] as has been pointed out recently [4]. This is especially true for results obtained from studies in cell lines that do not automatically reflect the reality of tumor biology as, for example, shown in ovarian cancer cell lines [5]. Although many papers investigated DNA, microRNA, epigenetics and proteomics had been published, there is 'no evidence whether this DNA originates from dying "normal" cells or from cancer cells or from both [4].

There is little doubt that the knowledge of mutations and genetics have brought about a deeper understanding of biology, and of cancer biology in particular. However, an important distinction lies in whether mutations that are observed in tumor samples have been consistently misinterpreted as being the cause of the underlying malignancy. Hereditary cancers occur in some 10% of all cancers and genetically triggered primary cancers represent some 8% of breast and ovarian cancers, which are causally linked to genetic changes such as breast cancer 1, early onset (BRCA1) or breast cancer 2, early onset (BRCA2) mutations; the corresponding figure for gastric cancer is less than 1%, for colorectal cancers it is somewhere between 3 and 5%,and infection-associated cancers are estimated to represent some 15% of all cancers [6-8]. Even these estimates seem misleading since no one knows why this ratio is about 60% in gastric cancers with *Helicobacter pylori* (*H. pylori*) infection and as high as 80% in liver cancers with chronic Hepatitis B or C viruses [9]. Therefore, broadly speaking about 80% of cancers are referred to as being 'sporadic', meaning their cause remains unknown.

It should come as no surprise, therefore, that somatic mutations are questioned as representing "the" cause for the majority of cancers [10, 11] and it should be noted that some cancers are not associated with any mutations whatsoever [12, 13]. De novo mutations in germline cells can be associated with "…rare and common forms of neurodevelopmental diseases, including intellectual disability, autism and schizophrenia" [14], and do not affect the discussion of the somatic mutation theory and carcinogenesis. Otherwise "hybrid viral-transposon systems" may serve as a mechanistic explanation for cancer genomes in higher eukaryotes which are not accessible to germline transgenesis by insertional mutagenesis [15].

The SMT follows other well-worn theories in medicine that, upon closer scrutiny were found to be associated with, but not causally related to, the disease in question. Many of these paradigms occurred from the incorrect interpretations of clinical observations resulting in ineffective clinical practice guidelines [16]. The missing explanation for some 80% of sporadic cancers was recently proposed as a hypothesis which considered biochemical and physiological processes, communication between cells and cell-cell signaling [17, 18]. A more nuanced view on the SMT and carcinogenesis, why genes are not just blueprints, radiation-induced mutations, the recent paper on why cancer may be a result of just 'bad luck' and *in vitro* and *in vivo* evidence justifying the questioning of the SMT are reviewed here.

Somatic mutation theory

The basis for the SMT hypothesis originated in 1914 when Theodor Boveri postulated that a combination of chromosomal defects could result in cancer [19]. This was followed by the

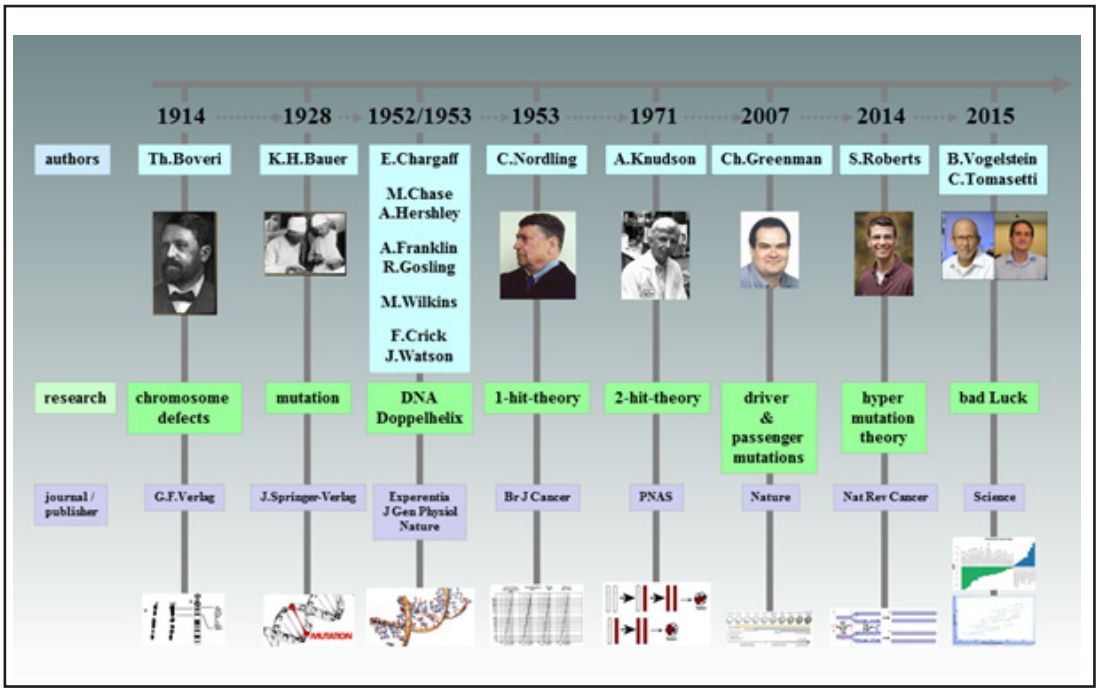

Fig. 1. 100 years somatic mutation theory.

proposal by Karl-Heinrich Bauer that mutations could cause cancer [20]. A milestone during the 1950s was the discovery of the DNA double helix and the genetic information revolution [21]. The noble laureate paper by Watson and Crick [22] was a "theoretical conversation…. with…..little experimental activity" [23] which was based on findings from Erwin Chargaff [24], Alfred Hershley and Martha Chase [25] and the X-ray diffraction study of DNA by Rosalyn Franklin and Raymon Gosling [26]. This led to the discovery of the polymerase chain reaction (PCR) in 1955 by Kleppe and Moulineux and its important modification by Mullis in 1983 [27, 28] – a clear revolution of biology and science [29]. However, it was the Finnish architect and urban planner, Carl O. Nordling, who worked through the age-specific cancer mortalities from statistic reports from the USA, UK, France and Norway and suggested that a number of mutated genes could cause cancerous cells to form cancer [30]. Ashley stated in 1969 that cancer may be the result of about 3 to 7 mutations [31]. Based on 48 cases of retinoblastoma, Alfred Knudson modified this mutational theory by proposing that a cell would need just one hit (mutation) and that could result in the mutated cell, by cloning, form a tumor [32]. It is noteworthy that Carl O. Nordling was even not cited. Later, the 1-hit theory was deemed to be too simplistic and was changed into a 2-hit theory in that a person who inherits a mutant allele must experience a second somatic mutation to initiate carcinogenesis. Some 25 years ago scientists reminded us that mutational changes in general would be insufficient to cause cancer and repeated Ashley's suggestion that at least 4 or 5 mutations might be necessary for such a 'cancer-initiating hit' (CIH) [33].

Even today, some 60 years after Carl O. Nordling's hypothesis, there are on-going attempts to force-fit the SMT hypothesis by proposing that three mutations are required to cause lung or colorectal cancer [34] and even postulate that cancer might require a 'hyper-mutation' event [35]. Large-scale sequencing studies have revealed that an even greater number of mutations might be necessary for causing the disease we call "cancer" [36]. Myelodysplastic syndrome (MDS) is used as a prime example of the veracity of the SMT by its proponents but we have learned that risk stratification is needed and that the evolution of risk for leukemia is "...less than 10% at 15 years for patients with low-risk MDS compared with more than 50% at 1 year for those with high-risk disease" [37]. Further acute lymphoblastic leukemia (ALL) is thought of as being caused by genetic factors, such as mutations or polymorphisms and environmental exposures; a minority of ALL in children was associated with polymorphisms

of rs17251221, rs4946936 or rs6214 and rs6218 in the 3'UTR of insulin-like growth factor 1 (IGF1) [38-40]. Recently it was shown, that ALL cases are not inherited. *In vivo* genetic evidence uncovered the causal role of infection exposure in acute lymphoblastic B-cell leukemia (B-cell ALL) as B-precursor acute lymphoblastic leukemia was only initiated if Pax5- inherited mice were exposed to common pathogenic stimuli. Furthermore, mutations of Janus-activated kinase 3 (JAK-3) occur *after* carcinogenesis is already underway [41]. This evidence supports the view that somatic mutations are epiphenomena and/or post-carcinogenesis events that clonally propagate cancer cells [17, 18]. Given that little by way of patient outcomes has emerged from the SMT, proponents have in recent years added the concept of 'driver' and 'passenger' mutations [42] in addition to the "hyper-mutation" theory [35] to patch over the weak links in the original SMT.

Cancer is not just one aberrant cell and one disease - cancer is a collection of more than 100 diseases with some traits in common [43]. Only a few cases have been associated with one important signalling pathway (e.g., Bcr-Abl tyrosine kinase in chronic myelogenous leukaemia, CML), which has allowed for the deployment of targeted therapy [44]. However, those same targeted therapeutic approaches are subverted over time as resistance develops rendering the treatment less effective and occasionally completely ineffective. A potential way of overcoming resistance against the tyrosine kinase inhibitor, gefitinib, has been recently shown to be effective *in vitro* by the use of Melatonin (N-acetyl-5-methoxytryptamine) [45].

An adult human contains trillions of cells of more than 200 types [46]. The one cell that can ultimately create every other type of cell in the body is enshrined in the fertilized ovum. It is known that normal cells can acquire mostly harmless mutations in the course of development from a single fertilized egg to an adult mammal. In fact, the term, 'post-zygotic mosaicism' was coined as a unifying term for all DNA changes acquired during life from single base pair mutations to aberrations at the chromosomal level [47]. It was further demonstrated that the post-zygotic genome is dynamic and that post-zygotic mutations represent a hitherto underestimated source of variation responsible for the development of human phenotypes that are not heritable and which cannot explain 'the 'missing heritability' [47]. Forsberg et al., recently suggested that the "weight should shift to the non-inherited component which, until now, has routinely been thought of as synonymous with environmental factors" [47].

Importantly, a detailed analysis of 31,717 cancer cases and 26,136 cancer-free controls from 13 genome-wide association studies [48] revealed that "the vast majority, if not all, of aberrations that were observed in the cancer-affected cohort were also seen in cancer-free subjects, although at lower frequency" [47]. Thus, the notion that somatic mutations are necessarily harmful and can lead to cancer is not borne out by this study and further affirms the hypothesis that mutations observed in cancers are not the triggering event but more likely a means for the clonal replication of already transformed cancer cells.

One would expect scientists to reevaluate the original paradigm given its inability to show appreciable clinical benefits over the past several decades. Taken together, the small percentage rates of proven somatic mutations which are indeed causative for a minority of hereditary cancers with the misinterpretation of higher rates of somatic mutations in more advanced stages of cancer, the extrapolation to most cancers from this dataset has confounded cancer biology and carcinogenesis resulting in a conflation of cancer biology that appears unwarranted. It seems logical that somatic mutations are epiphenomena and/or post-carcinogenesis events [17, 18].

Genes are not blueprints

Ever since Watson and Crick [22], many chronic diseases were thought reflexively to be caused by mutations even though we know that genes are an assemblage of alphabets that can, under non-genetic influence, be used to assemble a wide variety of proteins [49-51]. Since no-one still speaks, hears, or even understands the molecular words, sentences,

or language of genetic information – they result in silent insight [52]. Further, genes are not just blueprints as there is not only an inside-to-outside communication but also an outside-to-inside communication [4]. About 98% of the total human genome consists of non-coding DNA implying that only some 1-2 % of the total human DNA has been investigated with regard to its functionality. Even mobile DNA represents more than 40% of the total genome.

Recently, scientists searched for DNA mutations in 800 cancer patients (some 200 different cancer types) and compared the tumor DNA with the DNA of healthy cells of the same patients [53]. They reported that mutations found in cancer patients were correctly interpreted in the abstract as associated with the different cancer types [53] yet the results were misinterpreted in media interviews as though the authors had concluded that such observed mutations actually *caused* the observed cancers [54].

Long non-coding RNAs (lncRNAs), including their mutations, have been associated with cancer. As IncRNAs mediate repressor occlusion which include cyclooxygenase-2 (=Prostaglandin G/H synthetase 2, =COX-2), lncRNAs and PACER have been suggested as new targets for COX-2-modulation in inflammation and cancer [55]. However, IncRNAs and the proximity of spatial alleles are necessary for regulating genes [56] and the complexity of physiological homoeostasis and pathophysiology by multiple cellular processes regulating gene function(s) remains incompletely understood. Even mitochondrial DNA transfers between cells are a common physiological process for overcoming DNA damage rather than a pathological event [57]. Furthermore, there is growing evidence that knowledge of the genetic architecture is necessary to elucidate the role of genes which may act differently under different conditions [58]. Sea urchins are echinoderms which originated some 540 million years ago and it was shown by the Sea Urchin Genome Sequencing Project (SUGSP) Consortium that this species has genes for sensory proteins that are involved in vision and hearing in humans although the sea urchin itself has no eyes or ears [59]. Even the apolipoprotein B mRNA-editing enzyme's catalytic polypeptide 3 (APOBEC3) can mutate antibodies by an as yet unidentified mechanism [60].

Measurements of mutagenesis of cells grown in culture yield values of approximately 2×10^{-10} single base substitutions/nucleotide/cell division or 1×10^{-7} mutations/gene/cell division; an even lower number has been demonstrated in stem cells in culture [61, 62]. By comparison, the magnitude of DNA damage that occurs routinely during normal cellular processes is enormous. It has been estimated that approximately 10^4 depurinated sites are generated per cell per day and an even larger number of alterations result from reactive oxygen species (ROS) [63, 64]. Even if one were to assume that cancer arose in a single stem cell, then the spontaneous mutation rate would only be adequate to account for less than one mutation per tumor which led some to propose the hypothesis of a "*mutator phenotype*", wherein many more mutations may occur through the induction of genetic instability, a hypothesis not yet proven [65]. Investigations using retroviral insertion of mutagens in mice have shown that more than 2,000 genes must be mutated to contribute to cancer development [66]. This illustrates the wide variability in somatic mutations and the discrepancy between mutations required to cause cancer versus the large numbers of mutations that occur physiologically and which do not result in cancers. Aging has long been believed to be a major factor for the accumulation of somatic mutations resulting in a higher incidence of cancers as the animals ages but even this concept is now being questioned as the finite lifespan of hematopoietic stem cells (HSCs), rather than mutations, may lead to hematopoietic clonal evolution at extreme ages [67].

Moreover, signaling between hematopoietic stem and hematopoietic stem progenitor cells (HSPC) are different phenomena as was shown recently: nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling is the molecular component underlying the observed differences between HSPC and PBL [68]. NF-κB activation has been reviewed [17, 18] and shown to be activated by stromal cell-related cytokines of inflammation such as tumor necrosis factor alpha (TNF-α) [69]. It has also been shown that ROS activate NF-κB and this decreases tumor suppressor genes and increases oncogenes [17, 18, 70] with C-X-C chemokine receptor type 4 (CXCR4) expression independent of stromal cell-derived

factor 1 (SDF-1; synonym CXCL12) [71]. However, to date the clinical benefit of antioxidants in the prevention or treatment of cancers remains unproven. Other oncogenes, such as the Kirsten rat sarcoma viral oncogene (KRAS), are thought to be linked to carcinogenesis in cells after being implanted in immune-deficient mice [72]; It is presently not understood why KRAS is not 100% effective in mouse models [reviewed in 4]. One aspect could be that this is influenced by other genes, such as the Wilms' tumor gene (WT1), with its downstream target (*cMYC*) investigated in non-small cell lung cancer (NSCLC) [73]; however, WT1 alone has at leat some 24 isoforms.

Radiation – Mutation

Exposure to ionizing radiation causes cancer and this was seen early on as lending credence to the SMT since radiation was known to cause DNA damage. However, the different leukemia incidences with different dose-response curves for Hiroshima and Nagasaki after the two different types of A-bombs were dropped provides a different explanation. In Hiroshima, a linear dose-response curve was observed in leukemia incidence as the ionizing radiation in the bomb dropped there was of a high linear energy transfer (LET) type which caused double strand breaks in DNA such that the repair enzymes had no template to use to repair the damaged DNA [74]. In contrast, the bomb dropped over Nagasaki released low-LET radiation which primarily caused single-strand DNA damage and the repair enzymes were able to use the intact strand as a template to repair the DNA damage. Thus, the dose-response curve for leukemia in Nagasaki was S-shaped (as it is true for most non-carcinogenic chemicals and pharmaceuticals) [75]. If we apply this information on somatic mutations to radiation-induced cancers, only agents that cause double-strand DNA breakage become clinically relevant, unless one has defective DNA repair enzymes as in children with the autosomal recessive condition known as Xeroderma pigmentosum [76, 77]. In most non-hereditary cancers, the somatic mutations appear only after a normal cell becomes a cancerous cell and this allows the cancer cell to multiply in a clonal fashion. Neither the 1-hit nor the 2-hit nor the hyper-mutator phenotype theories account for the role of the DNA repair systems nor do they account for epigenetic modifications that protect against an even higher incidence of cancers than observed.

Cancer and bad luck

The most recent version of the SMT proposed that one's odds of getting cancer was a statistical event attributed to 'bad luck' through the accumulation of "enough" mutations to cause cancer [78]. If we remind ourselves about the percentages of cancers unquestionably attributed to mutations discussed above (about 5% of all cancers), we recognize that only a minority of cancers are triggered by mutations [6-8]. The "bad luck" thesis lacks, as the basis for the authors' stochastic model, several facts that appear to have been papered over. These include, 1) the theory that mutations cause cancer, and 2) that the risk of mutations is relatively constant for a given number of cell divisions. As pointed out above, the SMT is valid for some 5% of *hereditary* cancers, and from this alone it is clear that this model with its calculations and conclusions cannot be applied to the majority of non-hereditary cancers. Therefore, mathematically, the bad luck paper presents an untenable model as it can only apply to a small fraction of all cancers and confounds cancer biology with regard to its inapplicability to the vast majority of cancers.

Questioning the dogma

Recently the dogma of the SMT was deconstructed and the debate of the origin of cancer reignited by a new more plausible hypothesis for the majority of cancers by incorporating findings from both the plant and animal kingdoms, and by including clinical data to spell

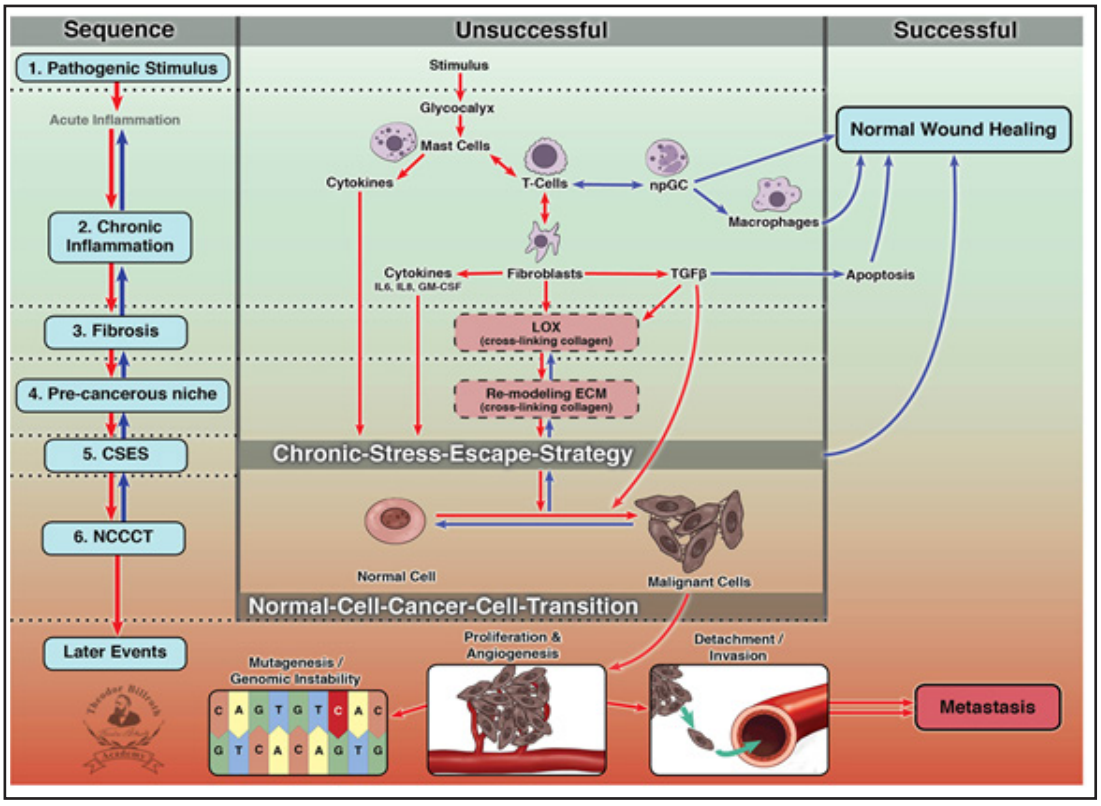

Fig. 2. Multistep carcinogenesis sequences– Epistemology of the origin of cancer [modified according to 17].

out that the following six steps are necessary for a normal cell to become a cancer cell: (1) a pathogenic stimulus (biological or chemical) followed by (2) chronic inflammation, from which develops (3) fibrosis with associated changes in the cellular microenvironment. From these changes a (4) pre-cancerous niche develops which triggers the deployment of (5) a chronic stress escape strategy, and when this fails to resolve, (6) the change of a normal cell to a cancer cell occurs [17, 18].

In vitro and *in vivo* evidence

The association of human papilloma virus (HPV) as the pathogenic stimulus for inducing cancer of the cervix was discovered in 1983 and by 1999 had been shown to cause nearly all cervical cancers. Human papilloma virus type 16 (HPV16) was initially reported in 11 out of 18 cancer patients in samples from Kenya and Brazil, and in vulva and penile cancer biopsy samples, but only rarely in condylomata accuminata (2/33) [79]. In 1986, cases of condylomatous dysplasia with severe stromal inflammation were negative for HPV more frequently than those with mild stromal inflammation [80]. This was subsequently discussed as an explanation for spontaneous regression. In such cases a T-cell phenotype linked inflammation was observed. Moreover, this investigation revealed that T-cell mediated immune reaction against cells, and not the HPV antigen, induced a systemic spontaneous regression of numerous flat warts in humans before cancer could develop. In 1999, HPV was reported in 93% of invasive cervical cancers [81]. Today we know that about 45% of women in the USA between the ages of 20 and 24 years are HPV-positive, an infection known to induce sub-clinical inflammation [82] and such sub-clinical inflammation was also reported in HPV-associated middle ear carcinoma [83] and in penile carcinomas likely by activation of pro-inflammatory cytokines [84, 85]. Recently, HPV was associated with colorectal cancer [86, 87], breast cancer [88] and with esophageal squamous cell carcinoma (ESCC) [89].

Chronic inflammation is an important step in the recently proposed six-step sequence to explain carcinogenesis anew [17, 18]. The continuous activation of tumor growth factor-beta (TGF-β) activates TGF-β-activated kinase 1 (TAK1/MEK)-mediated Akt resulting in persistent NF-κB activation [90] and, which in turn, induces cell proliferation. In 2008, it was shown that matrix metalloproteinase-7 [MMP7; synonym: pump-1 protease (PUMP1, uterine metalloproteinase or Matrilysn] is overexpressed in gastric pre- cancerous and cancerous tissue and that Helicobacter cytotoxin-associated gene (+) selectively increases MMP-7 both *in vitro* and *in vivo* [91]. Recently, the same group showed that MMP-7 knockdown mice showed less MMP-7 and increased H.pylori-induced gastric inflammation [92]. All knockdown mice showed increased gastric inflammation and the decreased MMP-7 levels were associated with increased M1 macrophage (a source of inflammation) markers. This was then scrutinized by transfection of H.pylori strain, PMSS1. The authors reported that both hyperplasia and dysplasia were increased in these knockdown mice.

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that regulate tumor suppression [93]. Several MMPs such as MMP-1, MMP-2, MMP-7 MMP-9, MMP-12 and MMP-14 interacts with the extra cellular matrix (ECM) enabling tumor invasion [94]. TGF-β was found to be a potent inducer of MMP-2 and MMP-9 expression in a Smad3- and Smad4-dependent manner [95] as well as the invasive phenotype in MDA-MB-231 cells, which was associated with TGF-β/Smad and TGF-β /ERK signaling [96].

The expression profiles of some MMPs have been correlated with poor clinical prognosis for several human tumors [97]. Historically, MMPs are thought to exert both pro-invasive and pro-metastatic activities by affecting remodeling of ECM [98]. ADAM-10 is a disintegrin (functions as an inhibitor of Integrin-dependent cell adhesion) and a metalloproteinase domain-containing protein 10. Under certain experimental conditions ADAM-10 can be inhibited [99] and behaves as tissue inhibitor of metalloproteinases-1 (TIMP-1) [100]. Adenovirus mediated TIMP-1 can reduce tumor cell invasion [101, 102]. MMPs are locally active at cell membranes if they are not inhibited by TIMP [103].

MMP-7was discovered in the uterus by Woessner [104]. MMP-7 breaks down the ECM by degrading casein, fibronectin, or collagen types I, II, IV and V [105]. MMP-7 has the ability to promote lung colonization of chondrosarcomas *in vivo* [106], was shown to be overexpressed in advanced colorectal polyps with severe dysplasia, and to facilitate their conversion to malignant cells [107]. MMP-7 appears to contribute to tumor aggressiveness as it is overexpressed at the invasion front of the tumor [108]. The expression of MMP-7 is regulated by the Wnt/β-catenin pathway and mediated by TGF-β [92] which may explain why MMP-7 is up-regulated in H.pylori infections [109]. TGF-β stimulates MMP-7 facilitating invasive behavior [103].

TGF-β induces MMP-9 production and activity. TGF-β mediated amplification of MMP-9 was attenuated by knockdown of a MYC-interacting transcriptional modulator Cited2 (CBP/p300-interacting transactivators with glutamic acid (E)/aspartic acid (D)-rich C-terminal domain) in a breast cancer cell line (MDA-MB-231 cells) [110]. Further it was shown, that TGF-β promotes MMP-9 mediated cancer cell invasion through SNAIL [111]. Thus, amplification of MMP-9 levels was shown to promote the destruction of the ECM and to increase the migration of inflammatory cells [112] while also playing a role in breast cancer invasion and metastasis through the degradation of type IV collagen-rich ECM [113].

Chronic inflammation results in continuous release of TGF-β with many consequent effects [17, 18]. E-cadherin and occludin are repressed by TGF-β increasing the adherens junction disassembly [114]. Invasiveness can be decreased by inhibiting TGFβ receptor type-I [115]. MiR21 is one key regulator of the mesenchymal phenotype transition and is induced by TGF-β [116], and increased levels have also been observed early in chronic fibrosis in chronic obstructive pulmonary disease (COPD) patients [117].

Lysyl oxidase (LOX) modulates the ECM and also affects cell migration and growth [118] and LOX-2 is critical to tumor microenvironment (and metastatic niche formation in hepatocellular carcinoma) [119]. Fibrosis is linked to TGF-β-integrin signaling in cancer [120] and was shown to be reversed by Relaxin and LOX-inhibitor therapy [121]. The pro-

inflammatory microenvironment reported recently in observations of HPV and colorectal cancer tissues [86], breast cancer [87, 88] and esophageal cancer [89] may lead to a pre-cancerous niche (PCN) [17, 18]. Furthermore, TGF-β induces LOX and MMPs [122], and LOX itself activates phosphoinositide-3 kinase (PI3K) [123]. SNAIL is stabilized by the protein kinase B (AKT) induced phosphorylation of glycogen synthase kinase-3beta (GSK3beta) [124], and this results in an increase of TGF-β-induced SNAIL [125]. LOX activates the stability and activity of SNAIL [126]. The long isoform p120 dissociates from the membrane and accumulates in the cytoplasm due to TGFβ [127, 128]. Taken together, these observations provide a plausible explanation for why the accumulation of p120 in the cytoplasm by chronic TGF-β release with its activation of LOX induces remodeling of the ECM forming the PCN, a process that may be seen as the starting point for the chronic-stress escape strategy as recently proposed [17, 18].

This serves as a plausible explanation for how chronic inflammation triggers fibrosis resulting in the formation of a PCN [17, 18]. Evidence why fibrosis, which results from chronic inflammation, is necessary for creating the PCN step comes from studies in the uniquely cancer resistant, long-living mole rat, the Spalax. Fibroblasts in this species suppress the growth of human cancer cells *in vitro* [129] and decrease the activity of hyaluronan synthase 2 [130]. As proposed earlier [17, 18] "…if a species (as Spalax) lives for about 30 years and does not develop cancer, even when exposed to known chemical carcinogens, this suggests that in the absence of the pre-cancerous niche, no cancer cells can gain a foothold ".

The connection between chronic inflammation that is capable of inducing fibrosis and which can then facilitate carcinogenesis is seen in Hepatitis B/C viral infection with consequent hepatocellular carcinoma (HCC) [17, 18, 131]. On the one hand this process seems dependent on a protein which is on the surface of white blood cells, the C-C chemokine receptor type 5 (CCR5 or CD195) [132], while on the other hand, it is dependent on TGF-β induced Smad phospho-isoform signaling [131]. Neutrophil granulocytes significantly influence the concentration gradient of chemokines such as the cytokine chemokine (C-X-C motif) ligand 1 (CXCL1). CXCL1 has neutrophil chemoattractant activity, is a potent angiogenic factor, and is expressed by macrophages, neutrophils and epithelial cells [133, 134]. Neutrophil granulocytes also regulate stromal interactions and were associated with worse prognoses in both breast and gastric cancers [135, 136].

In 2011, it was suggested, that circulating tumor cells (CTCs) in pulmonary veins during lung cancer surgery could be a prognostic indicator for early recurrence [137]. The same group showed that atrial natriuretic peptide (ANP) downregulates the inflammatory response and has a prophylactic effect on post-operative complications of lung surgery [138-140]. ANP, besides being an inhibitor of the renin-angiotensin-aldosterone pathway through specific binding to the guanylyl cyclase-A (GC-A) receptor also has an anti-fibrotic effect [141, 142]. The authors combined these findings during lung cancer surgery and treated lung cancer patients with "anti-inflammatory and anti-fibrotic" ANP and demonstrated that patients so treated exhibited lower recurrence rates [143].

Liver fluke (Opisthorchis viverrini) was shown to result in cholangiocarcinoma (CCC) in golden hamsters and in humans [144, 145]. Recently, it was shown, that Opisthorchis viverrini induces inflammation which *precedes* the CCC [146] lending support to the importance of inflammation in carcinogenesis.

The inhibition of vascular endothelial growth factor (VEGF) by neutralizing antibodies (mcr84) abrogated (1) the chemokine (C-X-C motif) ligand 9 (CXCL9) on mRNA and protein levels and (2) MMP-13 which are necessary for triggering fibrosis [147]. Fibrogenesis and tissue repair along with a resolution of fibrosis are promoted by VEGF which may explain why obesity and dysbiosis are associated with carcinogenesis. These observations along with the known fact that epidermal growth factor receptor (EGFR) induces MMP-7 and MMP-13 resulting in the progression of gastric cancers [148] could serve as an explanation for how the pathways come full circle.

Prostate adenoma as well as prostate inflammation is associated with prostate cancer; recently it was shown that chronic prostate inflammation in a mouse model of bacterial

inflammation resulted in increases of MMP-2, MMP-9 and LOX-induced fibrosis [149].

In 2006 it was shown that cell transition to specific cell lineages from adult mesenchymal stem cells was dependent on the matrix used and was facilitated by the use of transcription factors [150]. However, it was more recently shown that this might not be necessary insofar as cell lines growing in a matrix can result in high rates of reversion to stem-like cells and this could mean that pluripotency can be produced by modification of the ECM [151], a finding that remains to be replicated.

The transition from one cellular function to another, as well as the transition of one cell type to another is a routine event as opposed to a rare phenomenon [17, 18]. It has been shown that an epithelial mesenchymal transition (EMT) in embryogenesis/morphogenesis acts in a direction opposite to that of a mesenchymal-epithelial transition (MET) [152]. Furthermore, EMT can reportedly induce non-cancer stem cells to become cancer stem cells [153, 154]. It was also shown that chronic lung injury can result into a transition of a normal cell into a cancer cell [155].

AKT is activated through PI3K by TGFβ [156] resulting in activation of the targets of rapamycin complex 1 (mTORC1) and mTORC2 [157]. The PI3K/TmTORC1 pathway is also essential for cancer-associated inflammation [158]. Further, it was shown, that activation of PI3K/Akt and Erk through TGF-β mediated Syk and Src signaling resulted in EMT in human corneal epithelial cells (HCECs) *in vitro* initiated by Epstein-Barr virus (EBV)-associated keratitis [159]. Hypoxia-induced invasion and migration in cervical cancer cells mediated by the EMT were enhanced by LOX and inhibited by the LOX-inhibitor β-aminopropionitrile (BAPN) [160]. Sonic hedgehog (Shh) signaling is stimulated by TGF-β and regulates fibroblast function [161]. On the other hand, both EMT and Shh signaling are induced by TGF-β in bladder cancer [162]. Recently proteome profiling of urine samples from bladder cancer patients associated with *Schistosoma haematobium* infection [163] revealed further strong evidence of the proposed multi-sequence carcinogenesis process [17, 18].

Conclusions

The incorrect interpretation of data can sometimes appear to be the more parsimonious explanation especially when it has acquired the mantle of a paradigm, as in the case of the SMT. Summa Cancerologica is not hypothetical or ontological. Its syllogism of carcinogenesis needs the consideration of all reasonable perspectives such as whether somatic mutations are later events or epiphenomena occurring at the end of the sequence of events in carcinogenesis. This *mutatio praemissarum* leads to a reflection of reasoned judgments of correct findings in cancer (mutations within tumors) together with clinical observations (relevance of such mutations to cancer therapy). An overemphasis of the SMT as *the sole* reason of the origin of carcinogenesis elevated it to the status of a dogma which downplays significant findings of mutations and genetics in different fields of nature, biology and science. However, there is hope that hereditary cancers can be treated in the near future as new technologies make it possible to manipulate proteins packaging DNA to turn on specific gene promoters and enhancers [164]. If this were applicable to the mass of non-hereditary cancers this approach would still be only symptomatic as the genesis of non-hereditary cancers is not caused by somatic mutations though somatic mutations occur within tumors. Focusing on the tumor cell without its origin including the microenvironment won't be enough [165]. The reasoning on the origin of carcinogenesis, including different step-wise sequences, may help unmask mechanisms of the transition of a normal into a cancer cell (cancer genesis) as well as its different primary pathogenic stimulus, which can serve to prevent or retard cancers instead of concentrating on symptomatic strategies or for a cure for all cancers. It is scientifically valid based on *in vitro* and *in vivo* genetic findings that carcinogenesis consists of a six-step multi sequence process [17, 18]. This serves not just as a plausible alternative to the SMT to explain the origin of the majority of cancers, but could also suggest early interventions and thereby prevent the onset of cancer as a disease.

Abbreviations

ALL (acute lymphoblastic leukemia); ANP (atrial natriuretic peptide); APOBEC3B (apolipoprotein B mRA-editing enzyme, catalytic polypeptide-like 3B (= A3B)); Akt (protein kinase B); BAPN (β-aminopropionitrile); B-cell ALL (acute lymphoblastic B-cell leukemia); BRCA1 (breast cancer 1, early onset); BRCA2 (breast cancer 2, early onset); CCC (cholangiocarcinoma); CCR5 (C-C chemokine receptor type 5 (=CD195)); CIH (Cancer initiating hit); CML (chronic myelogeneous leukemia); COPD (chronic obstructive pulmonary disease); COX-2 (cyclooxygenase-2 (=Prostaglandin G/H synthetase 2)); CTCs (circulating tumor cells); CxCL1 (chemokine (C-X-C motif) ligand 1); CxCL9 (chemokine (C-X-C motif) ligand 9); CXCR4 (C-X-C chemokine receptor type 4); EBV (Epstein-Barr virus); ECM (extracellular matrix); EMT (epithelial-mesenchymal transition); ESCC (esophageal squamous cell carcinomas); GC-A (guanylyl cyclase-A); GSK3beta (glycogen synthasekinase-3beta); HCC (hepatocellular carcinoma); HCECs (human corneal epithelial cells); HPV (human papilloma virus); HPV16 (human papilloma virus type 16); HSCs (hematopoetic stem cells); IGF1 (insulin-like growth factor 1); IncRNAs (long non-coding RNAs); JAK-3 (Janus-activated kinase); LOX (lysyl oxidase); KRAS (Kirsten rat sarcoma viral oncogene); MET (mesenchymal-epithelial-transition); Melatonin (N-acetyl-5-methoxytryptamine); MMP (matrix metalloproteinase); MMP7 (matrix metalloproteinase-7); NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells); PCR (polymerase chain reaction); PCN (pre-cancerous niche); PI3K (Phosphoinositide-3 kinase); ROS (reactive oxygen species); SDF-1 (stromal cell-derived factor 1 (synonym CXCL12)); Shh (sonic hedgehog); SMT (somatic mutation theory); SUGSP (Sea Urchin Genome Sequencing Project); TAK1 (TGF-β-activated kinase 1); TGF-β (tumor growth factor-beta); TIMP-1 (Tissue inhibitor of metalloproteinase); TNF-α (tumor necrosis factor alpha); TORC1 (target of rapamycin complex 1); TORC2 (target of rapamycin complex 2); VEGF (vascular endothelial growth factor).

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Neither author has a competing interest to disclose.

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