

Norepinephrine release may play a critical role in the Warburg effect: an integrative model of tumorigenesis

Minireview

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Many cancer cells share the property of carrying out markedly elevated rates of glycolysis to generate energy even in the presence of sufficient oxygen, and this is known as the Warburg effect. In recent years, there has been a resurgence of interest in the Warburg effect, as the field of oncology has amassed evidence that cellular metabolism may play a prominent role in many neoplasms. Largely in the past decade, another prominent and perhaps surprising factor has emerged in the cancer literature: the catecholamine molecules, epinephrine (adrenaline) and norepinephrine (noradrenaline), appear to play a role in tumorigenesis and metastasis. The drug propranolol, which blocks beta-adrenergic receptors, may be therapeutic in human angiosarcoma, melanoma, and ovarian cancer. The current paper synthesizes these older and more recent findings, in an attempt to unify the major factors that contribute to tumorigenesis. This paper suggests that in addition to the direct interaction of catecholamine signaling with genetic risk factors (including mutagenesis), it interacts with environmental factors such as hypertension, obesity, unhealthy dietary components, physical inactivity, substance abuse, and mental or emotional stress, to promote the Warburg effect by facilitating glucose availability through suppression of pancreatic insulin release. Further, it proposes that many cancer cells synthesize and release catecholamines to activate their own receptors in an autocrine fashion. In summary, catecholamines are an important “new” factor in cancer that may interface with both genetics and environmental factors to alter the Warburg effect and modulate tumorigenesis.

Key words: beta-blocker, microenvironment, prazosin, pancreas, clonidine, guanfacine, genetics

Eminent German biochemist Otto Heinrich Warburg, who won the Nobel Prize in Physiology or Medicine in 1931 and made a wide range of seminal discoveries in his field, conducted experiments in the 1920s that led him to conclude that many if not all types of cancerous cells carry out a markedly elevated level of glycolysis [1–4]. This pattern of metabolism is puzzling because many cancer cells have adequate levels of oxygen to generate energy through the much more efficient process known as oxidative phosphorylation, which relies on intact mitochondria [5]. This metabolic phenomenon has been termed “aerobic glycolysis”, and it later became known as the Warburg effect [5, 6]. It is now known that some cancerous cells do not show elevated glycolysis, but the majority of cells do appear to exhibit this effect, and it has been suggested that blocking it could have anti-cancer effects [7].

The last several decades of research in oncology have been dominated by genetic and epigenetic models [8–12], but in recent years there has been a resurgence of interest in cellular metabolism in cancer, including the Warburg effect [13–15]. This is evident in research into the intracellular molecular mechanisms by which glucose is processed to contribute to the effect [16, 17]. Additionally, the diabetes drug metformin, which downregulates glucose signaling, is now being widely studied for its potentially therapeutic effects in various malignancies [18–20].

In the past decade or so, another signaling pathway has gained traction in the oncology literature: the sympathetic-adrenomedullary system comprising epinephrine (EPI; also known as adrenaline) and norepinephrine (NE; noradrenaline) [21–24], where these two catecholamines function as adrenal and sympathetic nervous system stress hormones

in the “fight-or-flight” response to environmental stressors or dangers [25–27]. NE in particular is an important neurotransmitter in the brain and at the output of the sympathetic nervous system, which comprises the set of peripheral nerves that regulate organs throughout the body. In an apparently serendipitous discovery around 2008, a group of French doctors published a paper suggesting the drug propranolol, which blocks beta-adrenoceptors (i.e., receptors that EPI and NE activate), can be used to shrink or eliminate benign tumors called infantile hemangiomas in newborns [28]. Since then a number of scientific papers have been published on this topic, and propranolol has become the first-line treatment for these tumors, clinically [29, 30].

Meanwhile, mainly within the past decade or so, a number of studies have suggested that propranolol is therapeutic in a range of cancer types (counteracting both tumorigenesis and metastasis, including in combination with other pharmacological agents), using *in vitro* preparations, *in vivo* rodent models, and retrospective epidemiological studies of human subjects [23, 31–34]. A fairly recent, prominent retrospective study found that non-selective beta-blocker (such as propranolol) use in women with ovarian cancer was associated with a median overall survival of 94.9 months, whereas non-users survived 42 months [35]. A prospective human subjects study found that propranolol protects individuals with thick cutaneous melanoma from disease recurrence [36].

A number of preclinical and clinical studies now also suggest favorable effects of propranolol on angiosarcoma, a difficult to treat malignancy with a poor prognosis [37–41]. There are also a number of ongoing clinical trials for propranolol in a variety of other neoplasms. Additional studies have suggested that NE itself promotes cancer [24, 42], and drugs other than propranolol that likewise block adrenoceptors, such as prazosin (which blocks the alpha1 adrenoceptor), are also therapeutic in rodent models [43]. Prazosin is already being used clinically to treat benign prostatic hyperplasia [44]. An additional point is that the molecules – serotonin, acetylcholine, and melatonin – may act centrally or interact with the sympathetic-adrenomedullary system in the periphery to modulate tumorigenesis and metastasis [45–47].

The rest of this paper integrates information about the Warburg effect and the “new” findings on sympathetic-adrenomedullary signaling, with the more well-established data on genetics and epigenetics in cancer. This framework also includes the following major environmental risk factors (which may additionally have a genetic component) for a broad range of neoplasms: hypertension, obesity (and associated dietary factors), physical inactivity, substance abuse, and (somewhat controversially) mental or emotional stress. I am suggesting here that elevated (partially genetic) sympathetic-adrenomedullary signaling plays a significant role in the development or manifestation of these risk factors, and

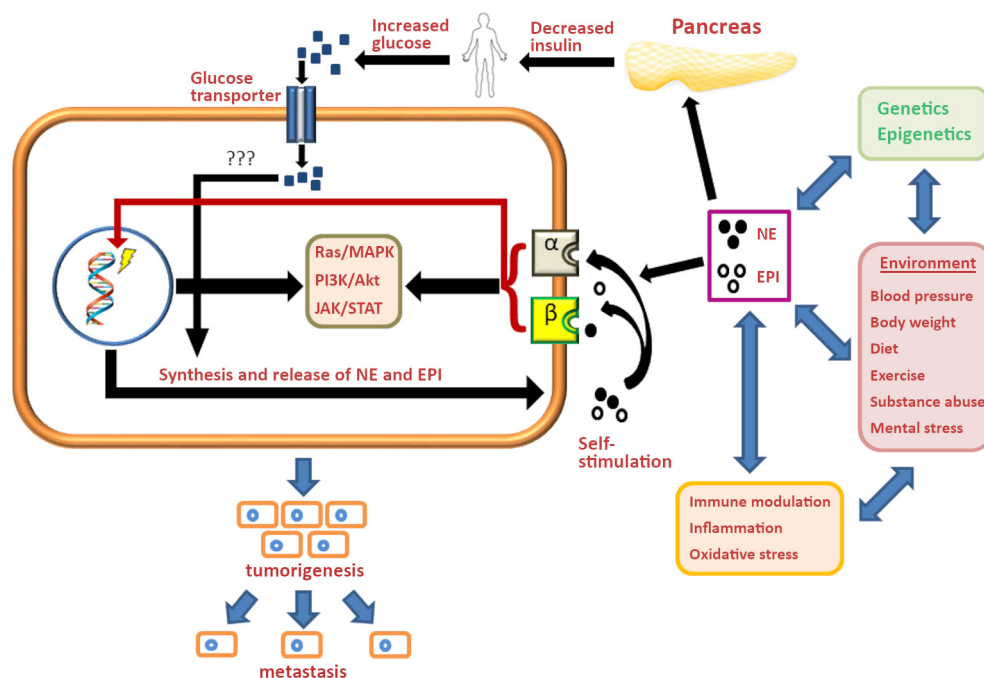


Figure 1. Proposed factors that contribute to tumorigenesis. In addition to the direct interaction of elevated central catecholamine release or peripheral sympathetic-adrenomedullary signaling with epigenetic and genetic risk factors (including mutagenesis), epinephrine (EPI) and norepinephrine (NE) interact with environmentally-regulated factors such as hypertension, obesity, unhealthy dietary components, physical inactivity, substance abuse, and mental or emotional stress, to promote the Warburg effect by facilitating glucose availability systemically through suppression of pancreatic insulin release (and perhaps by increasing insulin resistance). Further, this paper proposes that many cancer cells synthesize and release catecholamine molecules to activate their own alpha (α) and beta (β) adrenergic receptors in an autocrine fashion. EPI and NE may also interact with immune function, systemic inflammation, and oxidative stress to promote tumorigenesis and metastasis.

in doing so may play a critical role in the Warburg effect by promoting glycolysis, largely by helping supply glucose to the cancerous cells via suppression of insulin release by the pancreas. Those risk factors may in turn promote elevated sympathetic-adrenomedullary signaling.

Thus, in this model (Figure 1), cancer originates through a combination of genetic, epigenetic, and environmental factors over many years, usually including elevated sympathetic-adrenomedullary signaling throughout the process. (NE is also capable of causing mutations in DNA, further associating sympathetic-adrenomedullary signaling with the genetic component of cancer [48, 49]). Through these genetic and environmental factors, cancer cells may begin to selectively use glycolysis to fuel their growth and replication, and may also use glucose to help synthesize their own NE and EPI, which they release locally to stimulate their extracellular adrenoceptors in an autocrine fashion, thereby modulating the tumor microenvironment. This elevated sympathetic-adrenomedullary signaling, in turn, maintains or accentuates high levels of signaling in intracellular pathways that are already upregulated (and have previously been widely implicated in various neoplasms), such as Ras/MAPK, PI3K/Akt, and JAK/STAT, that fuel abnormal replication [50–53]. Thus, systemically elevated sympathetic-adrenomedullary signaling – that has existed chronically through genetic, epigenetic, and environmental mechanisms – may be complemented by additional cellular autocrine release. The rest of the paper briefly provides more detail on each of the components of the theory, integrating them with sympathetic-adrenomedullary signaling and the Warburg effect.

Genetics and epigenetics

For the last several decades, oncology research has focused on genetic mutations (or environmental phenomena that drive them) as the principal etiological factor in a broad range of cancer types [8–10]. For example, pioneering studies have identified a number of key oncogenes and tumor suppressor genes, that when mutated can help lead to tumorigenesis [54]. A potential connection of this literature with elevated sympathetic-adrenomedullary signaling is that NE and EPI themselves are able to induce DNA structural damage in a number of studies. For example, EPI and NE caused DNA damage in embryonic pluripotent cells via beta2 adrenoceptors [49], and NE also damaged DNA in human mammary epithelial MCF-10A cells [48]. Mental or emotional stress can also promote DNA damage, possibly by acting through NE [55]. I am not suggesting that NE (or EPI) is the main factor in mutagenesis, but rather that it is an important factor to consider, although most cancer-inducing mutations probably arise spontaneously or through other means. Also of note is that many of the mutated molecular pathways that can promote cancer – such as Ras/MAPK, PI3K/Akt, and JAK/STAT – have also been shown to be activated when NE or EPI bind to their G-protein-coupled

receptors (i.e., adrenoceptors) on the exterior (i.e., extracellular) surface of cells [50–53]. Thus, NE/EPI signaling and mutations arising from various means interact with the same molecular, protein-based pathways inside of the cancer cell, further reinforcing the idea that mutations as well as sympathetic-adrenomedullary signaling need to be considered in tumorigenesis. Another point of interest is that *epigenetic* mechanisms in cancer may also interface with sympathetic-adrenomedullary signaling: the histone deacetylase (HDAC) inhibitor drug, vorinostat, which modulates transcription of a number of genes, has been shown to increase cellular expression of the NE transporter (NET) molecule in the synapse [56]. Vorinostat and other HDAC inhibitors, such as valproic acid, are already being used clinically to treat subtypes of cancer [57, 58], and their principal therapeutic mechanism may be that by increasing expression of NET, they reduce the extracellular level of NE.

The genetics of the sympathetic-adrenomedullary system itself, independent of any mutations, may also play a prominent role in tumorigenesis and metastasis, perhaps in large part by facilitating the above three molecular pathways through signaling via adrenoceptors. Polymorphisms in the various genes comprising beta-adrenergic signaling could facilitate cancer by increasing the tone (i.e., overall chronic activation) of this system, while also amplifying ongoing acute responses to mental or emotional stress. A number of studies have already implicated beta-adrenergic genes in various malignancies, including interaction with environmental or other risk factors [59–62]. Polymorphisms in adrenoceptors, as well as the NE-synthesizing enzyme dopamine beta-hydroxylase, can modulate insulin resistance and alter glucose signaling [63–66], and may thereby influence the Warburg effect.

Hypertension

A number of studies, including epidemiological analyses as well as rodent data, suggest that hypertension (i.e., high blood pressure) is a risk factor for developing a number of types of neoplasms, although this is a controversial topic [67]. For example, spontaneously hypertensive rats (SHR) exhibited heightened sensitivity to the carcinogen, methylcholanthrene (MCA), which may be mediated in part by age-related deficits in T cell functioning, as well as elevated natural killer cell activity [68]. SHR also exhibited a greater frequency of chromosomal aberrations upon exposure to 7,12-dimethylbenz[a]-anthracene (DMBA) than control Wistar Kyoto rats [69]. Regarding human subjects data, a meta-analysis found a weak, albeit statistically significant, elevation in prostate cancer risk in men with hypertension [70]. A retrospective cohort study of Taiwanese subjects found that hypertension was associated with elevated rates of renal and uterine corpus cancers [71]. This ties in with a large body of evidence, including genetic and physiological studies, implicating elevated sympathetic-adrenomedullary signaling

in high blood pressure [72, 73]. For example, polymorphisms of beta-adrenoceptor genes are associated with hypertension [74], and SHR are known to exhibit elevated plasma NE [75]. Moreover, drugs that interfere with sympathetic-adrenomedullary signaling such as clonidine, propranolol, and prazosin, have long been used to treat high blood pressure clinically [76]. Thus, one possibility is that hypertension is a factor in various malignancies through elevated sympathetic-adrenomedullary signaling and its associated molecular processes [21], where this elevation may facilitate glucose signaling to enhance the Warburg effect, through suppression of insulin release by the pancreas as described below.

Obesity and metabolic syndrome

Being markedly overweight is also a risk factor for a number of cancer types. For example, obesity is associated with elevated risk or aggressiveness of colorectal [77], prostate [78], and breast [79] neoplasms. As for hypertension, there is an extensive literature, both in human subjects and animal models, linking obesity with elevated sympathetic-adrenomedullary signaling [80, 81]. For example, in healthy men, beta2 adrenoceptor polymorphisms associated with heightened sympathetic nervous system activity may predict future onset of obesity [82]. Rats fed a diet enriched in lard for four weeks exhibited 61% higher plasma NE relative to control animals fed regular chow [83]. Not surprisingly, there is also a known association between obesity and hypertension, and the two conditions coexist in many cases of metabolic syndrome, which itself is a major public health concern [84]. Metabolic syndrome is widely believed to be characterized by elevated sympathetic nervous system activity, further implicating sympathetic-adrenomedullary signaling in its pathophysiology [85]. Since one of the hallmarks of metabolic syndrome is insulin resistance, the disorder is further associated with elevated plasma glucose levels (since insulin, which is secreted by the pancreas, lowers blood glucose levels) [84, 86]. There are a number of physiological studies demonstrating that EPI suppresses insulin release from pancreatic beta cells [87]. Thus, hypertension, obesity, and also the often resulting condition of metabolic syndrome, are associated with elevated sympathetic-adrenomedullary signaling that raises systemic glucose levels and could thereby promote the Warburg effect in a number of organ systems and cell types throughout the body.

Dietary factors

Particular dietary factors, such as increased consumption of simple carbohydrates or foods high in saturated fat, could directly or indirectly boost glucose signaling to facilitate the Warburg effect, and chronically contribute to obesity and metabolic syndrome as well [88]. Significant consumption of high sucrose foods is associated with greater risk of colon [89], breast [90], lung [91], pancreatic [92], and endometrial

[93] cancer. Consumption of dietary sucrose is also associated with elevated noradrenergic and sympathetic-adrenomedullary signaling, both in human subjects and in rodents [94–96]. A high-fat diet also confers greater risk of colon [97, 98], breast [99], and prostate [100] neoplasms. This dietary factor is associated with elevated noradrenergic turnover and augmented sympathetic activity as well [83, 101, 102]. Finally, high sodium intake is associated in males with a greater risk of colorectal [103] and gastric [104] cancer; it likewise boosts plasma NE in spontaneously hypertensive rats [105] and can do the same in salt-sensitive human subjects [106]. In summary, dietary intake of significant amounts of sucrose, fats, and sodium confers greater risk for a number of cancer types, while also being associated with elevated noradrenergic signaling and sympathetic-adrenomedullary activation. Whereas intake of sucrose, which is a disaccharide consisting of a glucose and a fructose molecule, can directly boost glucose signaling to contribute to the Warburg effect, high fat or sodium intake (as well as sucrose consumption) boosts sympathetic-adrenomedullary signaling and could thereby indirectly contribute, possibly through pancreatic beta-cell modulation of insulin release.

Physical exercise

An adequate amount of physical exercise, perhaps aerobic exercise in particular, is associated with a number of health benefits, including a reduction in cancer risk, as well as improved survival in existing cases of cancer. For example, engaging in recreational physical activity is associated with a reduction in risk for breast [107, 108], colorectal [108], and lung [109] cancer. A number of studies suggest that exercise acutely boosts sympathetic-adrenomedullary signaling [110, 111]. Some studies suggest that repeated exercise, carried out over for example a number of weeks or months, *suppresses* sympathetic-adrenomedullary signaling both in animal models [112–115] and in humans [116], which is a possible mechanism for the reduced risk of developing or recurrence of cancer. Repeated exercise may also help counteract hypertension, obesity, metabolic syndrome, and insulin resistance – entities that may all be characterized by elevated sympathetic-adrenomedullary signaling – and may thereby reduce glucose signaling and oppose the Warburg effect.

Substance abuse

Substance abuse, particularly alcohol abuse and cigarette smoking, is associated with an increased risk of a number of cancer types, not limited to liver and lung neoplasms, respectively [117–119]. Although the molecular mechanisms underlying this effect on cancer risk are not well established, a broad range of substances of abuse, including alcohol and nicotine, acutely boost brain noradrenergic signaling (for review, see reference [120]). In the long-term, substance abuse may also be associated with chronically elevated

noradrenergic signaling, both in the brain and the periphery [120]. Hence, substance abuse represents another means through which increased central noradrenergic or sympathetic-adrenomedullary signaling may promote tumorigenesis, including through facilitation of glucose signaling.

Mental or emotional stress

Whether exposure to marked mental or emotional stress or trauma promotes cancer is a controversial topic. For example, a recent, large epidemiological study of breast cancer in Great Britain found only mixed evidence with regard to an increase in cancer risk [121], whereas three recent studies support a role for stress in breast cancer [122–124]. A recent meta-analysis of English and Scottish studies found that mental or emotional distress is a predictor of mortality in a variety of neoplasms [125]. Further, a Canadian epidemiological study found that men who reported higher levels of perceived stress in the workplace across a lifetime were at greater risk for neoplasms at five major sites of the body [126]. Data from rodent models provide strong evidence that mental or emotional stress promotes tumorigenesis and worsens overall survival [127, 128]. For example, Adamekova et al. found in female rats that seven consecutive days (120 min per day) immobilization stress, applied within the initiation phase of chemically-induced carcinogenesis, had a remarkable stimulatory effect on evaluated parameters in a breast carcinoma model. They found a marked 153% increase in tumor frequency per group, a 57% increase in tumor incidence, and a shortened latency period by seven days, all of which were statistically significant compared to controls [129].

As stated earlier, NE and EPI are “stress hormones” that are known to be released from cells, in the brain and the peripheral adrenal glands (as well as the sympathetic nervous system), as part of the fight-or-flight response to environmental threats or other aversive situations. Thus, exposure to trauma or marked mental or emotional stress, perhaps especially when such exposure is ongoing and chronic, may be another avenue through which elevated central or sympathetic-adrenomedullary signaling has deleterious effects on cancer onset, progression, or recurrence, perhaps in part by suppressing insulin production and promoting the Warburg effect.

Synthesis and autocrine release of NE and EPI

Another aspect of the overall hypothesis put forth in this paper is that many (but probably not all) cancer cells may synthesize their own pools of NE and EPI. One possibility is that such biosynthesis is facilitated by the increased availability of glucose. While biosynthesis of NE and EPI has historically been primarily localized to neurons in particular brainstem nuclei, cells in the adrenal glands, and sympathetic nerve endings, there are some data supporting catecholamine biosynthesis in other cell types, including immune cells [130,

131]. There are also findings from Schuller and colleagues that certain pancreatic and lung cancer cells synthesize their own NE, and then release it locally to stimulate their own extracellular adrenoceptors in an autocrine manner [132, 133] that modulates the tumor microenvironment. I am suggesting here that such a “self-stimulation loop” may be present in a wide range of cancer types, and it promotes signaling in already upregulated molecular pathways – such as Ras/MAPK, PI3K/Akt, and JAK/STAT – through adrenoceptor activation that sustains and facilitates further tumorigenesis and metastasis. One possibility is that NE increases glucose availability in the tumor microenvironment and beyond, and glucose availability may increase NE production in cancerous cells and possibly systemically, thereby potentially setting up a positive feedback loop that may be critical for tumorigenesis, growth, and metastasis. A recent osteosarcoma study found that NE is elevated in the tumor microenvironment relative to the adjacent and non-oncological bone, as are beta-adrenoceptors and the enzyme dopamine beta-hydroxylase which synthesizes NE [134]. A related point on the tumor microenvironment: viral-based cancers [135] may interact with local NE to promote tumorigenesis and metastasis.

Propranolol

There is increasing interest in using the non-selective beta-adrenoceptor (beta1 and beta2) blocking drug, propranolol, to prevent or treat various malignancies in human subjects [31, 41]. Cancer cells, in a given case, however, need not manufacture their own NE/EPI nor release it in an autocrine fashion to be susceptible to propranolol treatment, since this drug or related ones (carvedilol, nebivolol) may help lower blood sugar via modulation of insulin release by the pancreas or increasing insulin sensitivity [136, 137]. Propranolol and related beta-blockers may also improve glycemic control through modulation of GLUT4 glucose transporter expression and hexokinase-2, including in breast cancer cells [138–140]. In this scenario, propranolol could also block beta-adrenoceptors on the extracellular surface of the cancer cells, where these receptors would be responding to NE/EPI from others (i.e., non-autocrine) sources such as the adrenal glands. Cancer cells, in addition, need not exhibit the Warburg effect to be susceptible to propranolol (or related drugs): the drug could still block beta-adrenoceptors on the surface of these cells and thereby dampen intracellular molecular pathways associated with cancer. Also, if cancer cells exhibit the Warburg effect but do not have adrenoceptors, in a given case, they could still be susceptible to propranolol because this drug or related ones could still lower blood glucose via the pancreas or increase insulin sensitivity.

Summary and conclusions

As reviewed above, a wide range of genetic, epigenetic, and environmental factors may interact with central and

sympathetic-adrenomedullary pathways to modulate glucose signaling and thereby influence tumorigenesis and metastasis via the Warburg effect. Hypertension, obesity (and by extension, unhealthy dietary factors), physical inactivity, substance abuse, and recurrent mental or emotional stress – which may all be associated with chronically elevated sympathetic-adrenomedullary signaling – could promote cancer not only through the catecholaminergic lowering of insulin release (via pancreatic beta cells) or sensitivity to enhance systemic glucose signaling but also by NE and EPI binding to and activating adrenoceptors directly on cancer cells. Catecholaminergic autocrine signaling by cancer cells themselves may complement, in some individuals, already *genetically* elevated sympathetic-adrenomedullary tone that is present throughout the body and may also interact with the above environmental factors to promote malignancies. The beta-blocking drug propranolol already shows promising effects in a wide range of cancer types in human subjects, and other drugs that may lower catecholamine release or transmission – clonidine, guanfacine, dexmedetomidine, for example – should also be investigated in greater detail for their potentially therapeutic effects. The glucose modulating drug, metformin, which has been used clinically for years to treat diabetes, is gaining further traction for use in various neoplasms [18, 141], including in combination with propranolol [142]. Perhaps propranolol, metformin, and related catecholamine or glucose-modulating agents may not only attenuate the Warburg effect [143, 144] but also synergize with existing or emerging agents, such as in metronomic chemotherapy [39] or immunotherapy [145], to improve clinical outcomes.

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