Annals of Carcinogenesis

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Editorial

# Stabilization versus Ablation of Tumor Vasculature: Implications in Radio and Chemo-Sensitization

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**Received:** June 01, 2016; **Accepted:** June 02, 2016; **Published:** June 03, 2016

## Editorial

It is well established that tumors are unable to grow beyond certain size (1-2 mm) unless they acquire their own blood supply *via.* angiogenesis. In addition, angiogenesis helps tumors to invade adjacent tissues and metastasize to distant sites. Therefore, it has been postulated that interfering with the blood supply using anti-angiogenic therapies will destroy the tumor. However, there is an emerging alternative concept that depriving the tumor of its blood supply interferes with the delivery of chemotherapeutic agents to the tumor and creates unfavorable hypoxic environment that compromises the action of radiotherapy. This concept was supported by the modest responses to anti-angiogenic therapies in clinical trials and the lack of any impact on patient's survival when antiangiogenic drugs are administered as single agents [1]. Although, Hurwitz, *et al* [2] have shown that combining the antiangiogenic drug, Bevacizumab with chemotherapy significantly improved survival among metastatic colorectal cancer patients. Still, other studies demonstrated reductions in tumor concentrations of chemotherapy or effectiveness of radiotherapy when antiangiogenic drugs were co-administered [3-5]. Even when antiangiogenic drugs yielded significant effects on the growth of some tumors such as renal cell carcinoma, cervical cancer and ovarian cancer, they failed to demonstrate significant improvements in patients' survival [6,7]. Furthermore, complete resistance to antiangiogenic therapies have been reported for prostate and pancreatic adenocarcinoma and melanoma [8,9]. In order to explain this inconsistency, further research is needed for better understanding of the underlying cellular and molecular mechanisms of tumor vascularization and its interaction with cancer therapies in different tumor beds.

Tumors' blood vessels are often larger and more conspicuous than those of normal tissues [10]. However, tumors tend to actually have less blood supply than normal tissues because tumor blood vessels are fragile, leaky, morphologically abnormal and malfunctioning [11,12]. While the normal vasculature consists of evenly spaced, well-differentiated arteries, arterioles, capillaries, venules and veins, the tumor vasculature is heterogeneous, unevenly distributed and chaotic with a tortious irregular course that leads to zones of hypoxia and acidosis [13]. Tumors initiate a vascular supply through secreting angiogenic factors, mainly Vascular Endothelial Growth Factor (VEGF) [14]. Despite being of critical value in controlling the physiological processes of angiogenesis and vascular permeability [15], when continuously over-expressed in tumor tissues, VEGF induces accelerated and defective angiogenesis wherein vessels are immature, leaky, tortious and characterized by defective anatomy and physiology [16]. These structural abnormalities contribute to spatial and temporal heterogeneity in tumor blood function, resulting in poorly perfused and subsequently hypoxic tumor microenvironment. Targeting tumor vessels *via.* Anti-VEGF/VEGFR drugs have not been effective as a cure since impeding tumor blood supply deprives the tumor of oxygen, leading to hypoxia and acidosis that, in turn, can promote tumor growth, abnormal angiogenesis, and metastasis and also compromise the cytotoxic functions of immune cells that infiltrate tumors [17]. In addition, reduced tumor vascularity is a main contributor to therapeutic resistance in cancer since it interferes with the delivery of anti-cancer agents to the tumor targeted by chemotherapy or minimizes the production of Reactive Oxygen Species (ROS) in the tumor area, which is essential for radiation therapy induced cell killing [18,19]. Radiation-induced effects on cancer are brought about by inducing ROS production, DNA damage and apoptosis [20]. However, poor vascularization and hypoxia that characterize solid tumors induce resistance to radiotherapy and are positively correlated with more invasion and metastasis. This is achieved by two mechanisms: first, through the lack of $O_2$ and hence the interference with radiation-induced ROS production. Second, *via.* the hypoxia inducible factor-1α (HIF-1α) that provokes adaptive intracellular responses that, in turn, facilitate cell proliferation, interfere with apoptosis, provide protection from cell demise and ultimately rendering tumors radioresistant [21]. As a result, increasing the chemotherapeutic doses or strategies to intensify radiotherapy have been employed to increase the treatment efficacy. However, these procedures can potentially lead to a higher risk of serious side effects. To raise the therapeutic ratio (the ratio between the desirable cytotoxic effects and normal tissue complications), new strategies to enhance chemo and radiosensitivity of cancer are needed. To this end, we need to develop methods to improve tumor blood perfusion and normalize vascular development in order to increase tumor vulnerability to anti-cancer therapy as a better alternative to starving a tumor of its blood supply, which is not curative. Furthermore, one needs to emphasize that antiangiogenic drugs are not without side effects. Indeed, they have been reported to induce a myriad of toxic effects such as hypertension, hemorrhage, thromboembolism, proteinuria, malaise, fatigue, biochemical hypothyroidism, and cardiac failure, all are related to the non-specific action of antiangiogenic drugs that affects both normal and cancer tissues [1].

Tumor vasculature is functionally different than normal tissues'




**Citation:** Mahmoud AM and Ali MM. Stabilization versus Ablation of Tumor Vasculature: Implications in Radio and Chemo-Sensitization. Ann Carcinog. 2016; 1(1): 1001.

blood vessels. It is not simply the copious blood perfusion that induces tumor growth. Rather, enhanced tumor growth occurs in response to nurturing molecules produced by tumor-associated endothelial cells such as the unbalanced production of VEGF(s). However, due to the non-specificity of the current anti-VEFGF/VEGFR drugs and the treatment-resistant hypoxic environment subsequent to depriving the tumor of its blood supply, discovering new therapeutic targets in the tumor-associated endothelial cells is warranted. Recently, Notch receptor and its ligand Jagged-1 have been identified as key regulators of tumor angiogenesis. Studies on blocking notch and Jagged-1 signaling demonstrated tumor growth inhibition however this was accompanied by an increase in the number of non-functional vessels and poor tumor perfusion [22]. Thus, it is conceivable that ideal targets would be molecules or growth factors that are produced only by tumor-associated endothelial cells that can be blocked in order to normalize tumor vasculature without obstructing tumor blood supply, altering oxygen delivery or sheltering the tumor from chemotherapy.

In addition to over expressing tumor growth promoting factors, tumor-associated endothelial cells lack specific protein complexes that connect endothelial cells together such as the vascular endothelial adhesion molecule, VE-cadherin [23]. Alteration in these complexes causes leakage of fluid and molecules out of the vessels resulting in edema and hampers the delivery of cancer therapy to the tumor tissue which, in turn, contributes to cancer therapeutic resistance. Therefore, restoring VE-cadherin or other endothelial cell adhesion molecules in tumor-associated blood vessels could be a promising target for vascular normalization in cancer therapies. Besides direct targeting of angiogenic factors, an alternative recent approach involves modification of epigenetic processes. An emerging evidence supports a role of histone deacetylation and DNA methylation in the regulation of angiogenesis. Accordingly, several Histone Deacetylase (HDAC) and DNA Methyltransferase (DNMT) inhibitors are being examined for their anti-angiogenic properties [24]. Also, a new group of microRNAs (miRs) involved in cancer-related aberrant angiogenesis, hypoxia and cancer metastasis has been recently discovered. These miRs are referred to as angiomiRs and hypoxamiRs and they stand as promising new therapeutic targets in cancer [25].

A new venue that we believe is worth exploration is physical exercise as a non-pharmacological novel adjuvant therapy to normalize tumor blood vessels, restore their normal structure and function and subsequently increase tumor sensitivity to cancer therapy. The foundation of this assumption comes from the strong epidemiological and experimental evidence supporting the role of exercise in improving blood flow and tissue perfusion in normal and post-ischemic tissues [26-29]. Exercise elevates the intravascular shear stress which in turn activates endothelial cell production of vasodilators [30]. A number of vasodilators have been shown to increase in response to exercise however, two compounds stand out as central mediators of exercise action: Nitric Oxide (NO) and Prostacyclin [31]. Exercise-induced vasodilation increases tissue hyperemia and oxygenation which subsequently normalizes the microenvironment and induces the formation of new well-developed, normal-functioning blood vessels. This pro-angiogenic effect of exercise has been proposed to be mediated through several angiogenic factors such as VEGF, angiopoietin 1 and 2, PPAR gamma coactivator-1alpha, cAMP- and cGMP-independent smooth muscle relaxation [31-33]. Exercise has been shown to restore the balance between pro- and antiangiogenic factors which promotes a shift towards normalized tumor microenvironment.

Intriguingly, emerging data indicate that aerobic exercise improves tumor perfusion and cancer therapy efficacy and reduces tumor metastasis in preclinical prostate and breast cancer models [34-36]. In a prospective cohort of 571 men with prostate cancer, Van Blarigan, *et al* demonstrated that physical activity normalized tumor vessel density, size and shape [37]. Despite this progress in unraveling the effect of exercise in improving cancer perfusion and treatment sensitivity, we do not see exercise being recommended for cancer patients who are more likely to have complications that discourage them from exercising. Probably if more clinical trials succeeded to prove that exercise synergizes with cancer therapy, there would be a strong impetus for patients to exercise and for oncologists to recommend exercise for their patients.

In conclusion, it is imperative to understand the underpinnings of tumor vascularity and microenvironment. Tumor blood vessels, albeit malfunctioning, they are the portal to deliver drugs to cancer tissues thus, instead of targeting tumor vessels for elimination, functional enhancement might be tried instead. Identifying novel therapeutic targets and interventions to normalize tumor vascular bed should make it possible to enhance the efficacy of cancer chemo and radiotherapies.

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Ann Carcinog - Volume 1 Issue 1 - 2016
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**Citation:** Mahmoud AM and Ali MM. Stabilization versus Ablation of Tumor Vasculature: Implications in Radio and Chemo-Sensitization. Ann Carcinog. 2016; 1(1): 1001.