Thermal tumor ablation therapy: Implications in Radio and Chemo-sensitization

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Abstract
It is well established that tumors are unable to grow beyond a certain size (1-2 mm) unless they acquire their own blood supply via angiogenesis. Also, angiogenesis helps tumors to invade adjacent tissues and metastasize to distant sites [1]. Therefore, it has been postulated that interfering with the blood supply using anti-angiogenic therapies will destroy the tumor [2]. 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 an unfavorable hypoxic environment that compromises the action of radiotherapy [3]. 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 [4]. Although, Hurwitz et al. [5] 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 [6-8]. 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 [9,10]. Furthermore, complete resistance to antiangiogenic therapies has been reported for prostate and pancreatic adenocarcinoma and melanoma that might be attributed to the redundant involvement of several angiogenic factors that are difficult to be targeted by a single anti-angiogenic agent in some tumors [11-13]. 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.

Introduction
Tumors’ blood vessels are often larger and more conspicuous than those of normal tissues [14]. However, tumors tend actually to have less blood supply than normal tissues because tumor blood vessels are fragile, leaky, morphologically abnormal and malfunctioning [15,16]. 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 [17]. Tumors initiate a vascular supply through secreting angiogenic factors, mainly vascular endothelial growth factor [VEGF] [18]. Despite being of critical value in controlling the physiological processes of angiogenesis and vascular permeability [19], when continuously over-expressed in tumor tissues, VEGF induces accelerated, and defective angiogenesis wherein vessels are immature, leaky, tortuous and characterized by disturbed anatomy and physiology [20]. These structural abnormalities contribute to spatial and temporal heterogeneity in tumor blood function, resulting in poorly perfused and subsequently hypoxic tumor microenvironment. To date, no specific molecules have been shown to be expressed exclusively by tumor endothelial cells. However, several molecules are overexpressed in tumor endothelial cells compared with normal endothelium such as VEGF/VEGFR-2, integrins alpha v5 and alpha 5b1, endolgin, [CD105], thrombospondin-1 receptor [CD36], Thy-1, phosphatidylserine, prostate-specific membrane antigen [PSMA], and multiple tumor endothelial markers [TEMs] [21]. Such disturbances in these growth factors create a chaotic microenvironment that promotes unrestricted angiogenesis and vascular abnormalities.

Targeting tumor vessels
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, enhanced tumor growth, abnormal angiogenesis, and metastasis and also compromise the cytotoxic functions of immune cells that infiltrate tumors [22]. Reduced tumor vascularity is a primary contributor to therapeutic resistance in cancer since it interferes with the delivery of anti-cancer agents to the tumor targeted by chemotherapy and minimizes the production of reactive oxygen species (ROS) in the tumor area, which is essential for radiation therapy induced cell killing [23,24]. Radiation-induced effects on cancer are brought about by inducing ROS production, DNA damage and apoptosis [25]. However, poor vascularity and hypoxia that characterizes solid tumors cause resistance to radiotherapy and are positively correlated with more invasion and metastasis [15]. This effect is achieved by two mechanisms: first, through the lack of O2 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 [26]. The third mechanism that has been recently described in hypoxic tumor tissues is their ability to switch the mode of vascular formation from local sprouting angiogenesis to vasculogenesis which is the formation of blood vessels from circulating cells. This adaptive mechanism allows tumor tissues to evade the anti-angiogenic effect of radiation, rendering the tumor more resistant to radiotherapy [27]. As a result, increasing the chemotherapeutic doses or strategies to intensify radiotherapy has been employed to improve the treatment efficacy.
However, these procedures can potentially lead to a higher risk of severe side effects including significant endothelial cell apoptosis, reduction of vascular density and changes in vessel morphology which exacerbate the hypoxic condition in tumor tissues leading to a viscous circle of hypoxia and treatment resistance [28]. 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 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 [4].

Tumor vasculature is functionally different than normal tissues’ blood vessels. It is not merely 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-VEGF/VEGFR drugs and the treatment-resistant hypoxic environment after depriving the tumor of its blood supply, discovering new therapeutic targets in the tumor-associated endothelial cells is warranted [29]. 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 [30]. 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 to normalize tumor vascularity without obstructing tumor blood supply, altering oxygen delivery or sheltering the tumor from chemotherapy.

**Results**

In addition to overexpressing 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 [31]. Alteration in these complexes causes leakage of fluid and molecules out of the vessels resulting in edema and high interstitial pressure and hamper the delivery of cancer therapy and tumor-targeting lymphocytes to the tumor tissue which, in turn, contributes to cancer therapeutic resistance [32]. 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, a recent alternative approach involves modification of epigenetic processes. 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 [33]. 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 angi miRs and hypoxa miRs, and they stand as promising new therapeutic targets in cancer [34].

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 treatment. 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 [35-38]. Exercise elevates the intravascular shear stress which in turn activates endothelial cell production of vasodilators [39]. Some 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 [40]. 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, angioptin 1 and 2, PPARgamma coactivator-1alpha, cAMP- and cGMP-independent smooth muscle relaxation [40-42]. 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 [43-45]. 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 [46]. Hypoxia and its associated biomarkers have been recognized as independent predictors for aggressive behavior and therapeutic resistance in breast and prostate cancer as well as bladder, cervical and nasopharyngeal carcinomas. Thus, these types of cancer are expected to benefit the most from perfusion improving interventions [47]. 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 great boost for patients to exercise and for oncologists to recommend exercise for their patients.

**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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