Angiogenesis and the tumor space-time continuum.

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Tumors invade space through cancer cells proliferation and tumor mass expansion. Tumor growth is maintained over time using the cancer stem cell pool, which is the cell population with self-renewal potential. In their paper Conley et al. provide evidence that anti-angiogenic agents increase cancer stem cells through the generation of tumor hypoxia (1). These findings are in accordance with those demonstrating that hypoxia induces stem cell markers expression in cancer cells (2-4), and that anti-angiogenic therapy elicits malignant progression of tumors (5). Thus, there is now sufficient evidence to reconsider the role of tumor angiogenesis in cancer progression. Tissues need nutrients and oxygen for growth and tumor behaves as other tissues. This is the classical view, in which, according to Folkman, the role of tumor angiogenesis fulfills the function of normal vessels that is to deliver oxygen and metabolites and to remove waste products. However, tumor vessels are abnormal and fail to fulfill these functions. Therefore, tumors have naturally chronic and cyclic hypoxic regions. This is a paradoxical consequence of tumor angiogenesis, because of its deficiencies, also generates hypoxia. In pathology, such as cancer, a defect in a physiological process does not necessarily suppress the function of the process but can generate a novel function required for disease development. Here, the other function of tumor angiogenesis is to maintain tumor growth over time via cancer stem cell increase. This dual nature of tumor angiogenesis ensures a balance between growth over space (by providing oxygen and nutrients; i.e. physiological function), and growth over time (by generating hypoxic regions that increase the cancer stem cell pool; i.e. pathophysiological

function). Hence, tumor requires both the physiological and the pathophysiological functions of tumor angiogenesis. Therefore the significance of angiogenesis is the generation of a tumor space-time continuum.

1. Conley S, et al. (2012) Antiangiogenic agents increase breast cancer stem cells via generation of tumor hypoxia. *Proc Natl Acad Sci USA* 109:2784-2789.
2. Platet N, et al. (2007) Influence of oxygen tension on CD133 phenotype in human glioma cell cultures. *Cancer Lett* 258:286-290.
3. Mathieu J, et al. (2011) HIF induces human embryonic stem cell markers in cancer cells. *Cancer Res* 71:4640-4652.
4. Qiang L, et al. (2012) HIF-1α is critical for hypoxia-mediated maintenance of glioblastoma stem cells by activating Notch signaling pathway. *Cell Death Diff* 19:284-294.
5. Paez-Ribes M, et al. (2009) Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. *Cancer Cell* 15:220-231.