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# Probing The Regulation Of Vasculogenic Mimicry In Glioblastoma: Implications For Treatment In Patients



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Date of Award
5-2011

Document Type
Campus Access

Degree Name
Doctor of Philosophy

Degree Program
Molecular and Cellular Biology

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Keywords
Health and environmental sciences, Biological sciences, Angiogenesis, Anti-angiogenic treatment resistance, Cancer, Cancer stem cells, Glioblastoma, Vasculogenic mimicry

Subject Categories
Cell Biology | Medicine and Health | Molecular Biology

Abstract
Glioblastoma, previously known as Glioblastoma Multiforme (GBM), is a highly angiogenic tumor and is defined pathologically by its ability to create microvascular proliferations. Patients with glioblastoma have a high rate of morbidity and mortality because of the aggressive nature of this

type of tumor. Despite current optimal treatments, glioblastoma is almost universally fatal with the current median survival being between 12-15 months. The current treatment for glioblastoma involves surgical resection followed by chemotherapy and radiation. However, recently a new anti-angiogenic treatment called Bevacizumab (trade name Avastin) has been able to prolong survival, significantly in some cases. Some patients on this therapy have demonstrated wonderful responses, but in most cases, this response is transitory and there is eventual recurrence, thus highlighting that there could be resistance to anti-angiogenic therapies inherent within glioblastoma.

Here, it is proposed that this resistance is mediated by an alternative angiogenic pathway that is produced by glioblastoma stem-like cells. Through a trans-differentiation process, we have found that the vast majority of the vasculature (80%) acquires a mural cell phenotype that "mimics" the vasculature and creates a blood supply to the tumor. Although this process has been defined in other types of cancer as Vasculogenic Mimicry, this process has never been demonstrated to be due to mural cell involvement.

We have also identified and more fully characterized this alternative form of vasculogenesis by its dependence on a molecular pathway through which it is created and maintained in glioblastoma. We have found that the glioblastoma stem-like cells transdifferentiated *in vitro* , and *in vivo* in a Flk-1 (VEGFR2) dependent manner when transplanted into SCID/beige mice. When this receptor was knocked down in transdifferentiated glioblastoma stem-like cells, it inhibited tumor growth and development almost completely. Since current angiogenic therapies for glioblastoma do not target this form of vasculogenesis, it is hoped that this work will in part fill a void in the current research and create additional knowledge to help better guide treatment for these patients.