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“Targeting novel angiogenic factors related to AKT kinase activity in ependymoma”



Angiogenesis, or the formation of new blood vessels, is required by a growing cancer in order to sustain its growth. The biological mechanisms of angiogenesis have been intensively studied in the past 10-15 years, including studies in brain tumors. The studies have discovered some of the major mediators of angiogenesis, most notably vascular endothelial growth Factor, VEGF, which is produced by gliomas and other tumors in response to low oxygen levels (hypoxia). However, while VEGF induction of new blood vessels is prominent in rapidly growing adult brain tumors, this mediator may not play as prominent a role in certain pediatric brain tumors. The important mediators, and therefore molecular therapeutic targets, of angiogenesis in pediatric brain tumors such as ependymoma have not been studied in nearly as much detail, and remain poorly defined.



In recent genomics studies of childhood ependymomas, we have discovered a number of novel and potentially important angiogenesis-related proteins. These studies suggest an angiogenic balance exists in childhood ependymomas, involving novel protein mediators, which when better understood may be modulated therapeutically to more effectively treat childhood ependymoma.

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Novel mediators of angiogenesis in childhood ependymoma

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Angiogenesis, or the formation of new blood vessels, is required by a growing cancer in order to sustain its growth. The biological mechanisms of angiogenesis have been intensively studied in the past 10-15 years, including studies in brain tumors. The studies have discovered some of the major mediators of angiogenesis, most notably vascular endothelial growth Factor, VEGF, which is produced by gliomas and other tumors in response to low oxygen levels (hypoxia). However, while VEGF induction of new blood vessels is prominent in rapidly growing adult brain tumors, this mediator may not play as prominent a role in certain pediatric brain tumors. The important mediators, and therefore molecular therapeutic targets, of angiogenesis in pediatric brain tumors such as ependymoma have not been studied in nearly as much detail, and remain poorly defined. In recent genomics studies of childhood ependymomas, we have discovered a number of novel and potentially important angiogenesis-related proteins. One of these, Spondin-1, is highly expressed in a distinct subset of ependymomas that also bear over-expression of the oncogenic kinase AKT2. Because Spondin-1 plays an important role in development of the brain and spinal cord, has been reported to play a role in angiogenesis and has been recently identified as being related to poorer overall survival in certain cancers outside the brain, we are investigating whether this protein may be modulating the angiogenic potential of ependymomas. Several lines of experimentation have demonstrated that: 1) Spondin-1 expression is elevated during early development of the brain in rodents and then is greatly reduced in the adult brain; 2) Spondin-1 is variably expressed in human childhood ependymoma biopsy specimens and primary human ependymoma xenografts at both the RNA and functional protein levels, and is distinctly elevated in a subset of these tumors; and 3) Spondin-1 expression is tightly correlated with that of the AKT2 kinase. As a result of these findings, currently we are studying Spondin-1 expression in correlation with a number of other angiogenesis related proteins, and performing microvessel density studies, to gain more insight into the broader angiogenesis context by which Spondin-1 may influence tumor growth. Additionally, we are perturbing Spondin expression levels and the related AKT2 kinase to better understand the functional relationship between the two factors, as well as their impact on the behavior of tumor cells and adjacent blood vessels. These studies suggest an angiogenic balance exists in childhood ependymomas, involving novel protein mediators, which when better understood may be modulated therapeutically to more effectively treat childhood ependymoma.