Editorial

Tenascin-C induces expression of the Notch ligand Jagged1 to promote glioma growth

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Tenascin-C is an extracellular matrix glycoprotein with a dynamic and restricted distribution during organ development and in disease. Tenascin-C is up-regulated in response to several pathological conditions, including cancer, and a number of studies have implicated it in the regulation of glioma cell migration, invasion and angiogenesis. In a recent article published in the journal *Cancer Research*, Sarkar and colleagues present evidence indicating that Tenascin-C can also sustain proliferation of brain tumor initiating cells by promoting expression of the Notch ligand Jagged1 (1).

Tenascin-C promotes glioma aggressiveness

One major function of Tenascin-C during normal development is to modulate adhesion and migration of multiple cell types (2). In line with this, several studies have indicated that Tenascin-C is capable of regulating migration of glioma cells as well, thereby affecting their ability to invade surrounding brain tissue. Administration of purified Tenascin-C protein to glioma cell cultures enhances migration, whereas blocking anti-Tenascin-C antibodies or Tenascin-C knock-down have inhibitory effects on glioma cell migration and invasion (3-5). Mechanistically, Tenascin-C can act as a ligand for specific integrin receptors and could therefore potentially regulate migration via Itga7, one major integrin that promotes glioma invasion *in vivo* (2,6). It has also been proposed that Tenascin-C supports invasiveness in glioma by positively regulating the expression of matrix matalloproteinase 12 and a disintegrin and metalloproteinase 9, which in turn could contribute to extracellular matrix remodeling and Tenascin-C turnover in the tissue (7,8).

In addition to enhancing the migratory behavior of glioma cells, Tenascin-C can also promote glioma malignancy by affecting angiogenesis within the tumor. It has been shown that Tenascin-C triggers secretion of pro-angiogenic soluble factors including ephrin-B2 by glioma cell (9). This Tenascin-induced pro-angiogenic secretome correlates with more numerous but less functional blood vessels and poorer glioma patient survival (9).

Even though it has been previously proposed that Tenascin-C could be involved in the regulation of cell proliferation in glioma, its role in this context has remained somewhat controversial. Blocking anti-Tenascin-C antibodies reduced proliferation in gliolastoma cell cultures (5). However, Tenascin-C knock-down cells were more proliferative in a xenotransplantation model, suggesting that Tenascin-C favors migration at the expense of proliferation *in vivo* (4). In their recent study, Sarkar and colleagues now convincingly show that Tenascin-C can stimulate cell proliferation and colony formation of human glioma cell lines in neurosphere assays (1). The authors of this work present evidence that the effects of Tenascin-C are mediated by upregulation of the Notch ligand Jagged1 by tumor cells, suggesting that Tenascin-C exerts its pro-

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proliferative action via activation of Notch signaling, a critical regulator of stem cell fate and self-renewal in both healthy brain and brain tumors (1).

The Notch pathway controls neural stem cell (NSC) plasticity and can influence glioma formation

Notch signaling is fundamental for self-renewal of NSCs in the developing and adult brain (10). Notch transmembrane receptors bind their ligands presented on the surface of neighboring cells and are proteolytically cleaved releasing the Notch intracellular domain (NICD) in the signal receiving cell. Once in the cell nucleus, the NICD converts a transcriptional repressor complex into an activator thereby inducing the transcription of Notch target genes. Canonical Notch targets of the Hes/Hey family are expressed at high levels in NSCs and required for stem cell maintenance by repressing differentiation (10).

The presence of cancer stem cells that are able to differentiate into less-tumorigenic cancer cells that form the bulk of the tumor, is one phenomenon that can confer intratumoral heterogeneity and therapy resistance. Therefore, signaling pathways that promote stem cell features are promising targets for developing more effective cancer therapies. Altered Notch activity has been linked to many types of cancer, and expression of Notch signaling components has been detected in brain tumors. Interestingly, Notch signaling is restricted to subpopulations of tumor cells in glioma and it has been proposed to promote their stem cell character (11,12). *In vitro* and xenotransplantation studies showed that blocking Notch can reduce glioma cell survival and self-renewal as well as the presence of relatively quiescent and therapy resistant glioma cell subpopulations, thereby implicating Notch as an oncogenic pathway in this type of tumor (11-14). However, surprisingly, recent work revealed that Notch signaling can also act as a tumor suppressor in brain tumors. Genome-wide analysis of large patient cohorts with lower-grade gliomas identified mutations in the NOTCH1 and NOTCH2 genes in a significant proportion of the tumors (15,16). These mutations occurred at similar positions to those demonstrated experimentally to inactivate the Notch1 receptor in epithelial cancers (15,16). In line with these findings, high expression levels of specific Notch target genes positively correlate with longer survival in patients with lower-grade gliomas and glioblastoma subtypes (17). In addition, genetic inactivation of the Notch1 and Notch2 receptors or RBP-Jk, an indispensable mediator of the Notch signaling pathway, accelerated tumor growth in a PDGF-driven mouse model of glioma and, conversely, genetic activation of Notch increased survival of the mice (17). Thus, Notch signal inhibition may be an important molecular event in the formation of some forms of glioma. Overall, these data support the hypothesis that the role of Notch in glioma may be context-dependent and differ between glioma subtype and stage of tumor progression or recurrence after therapy (18).

Tenascin-C/Notch interaction in glioma growth

The work by Sarkar and colleagues reveals an important role of Tenascin-C in glioma cell self-renewal and proliferation (1). Among various extracellular matrix components tested, exogenously applied Tenascin-C had the strongest effect on cancer sphere formation and it increased the number of cells in S-phase in the cultures, indicating that Tenascin-C stimulates glioma proliferation (1). These effects on tumor cells may be reminiscent of one of the variegate functions of Tenascin-C during central nervous system development, where Tenascin-C regulates the responses of NSCs and oligodentrocyte progenitors to EGF and PDGF, respectively, and the formation of the postnatal neurogenic niche (19,20). Interestingly, Tenascin-C was not only expressed at high levels in glioma specimens *in vivo* but was directly produced by glioma cells *in vitro*, similar to in neural progenitor cultures and radial glia (2), and knocking-down Tenascin-C reduced cancer sphere formation, indicating an autocrine effect (1). It would be interesting to determine the relative contribution of Tenascin-C produced by tumor cells versus stromal cells, such as reactive astrocytes (21), to glioma growth *in vivo*.

Tenascin-C has many interaction partners and can control cell behavior both indirectly by binding extracellular matrix components and directly by interacting with cell surface receptors (2). Notably, blocking alpha2beta1 integrin by RNA-interference or with specific antibodies, abolishes the increase in glioma sphere formation induced by Tenascin-C, suggesting that alpha2beta1 acts as a Tenascin-C receptor (1). Integrin alpha7, a potential Tenascin-C interacting integrin (2), is also expressed by glioma cells and promotes their proliferation, survival and invasion (6). It would be interesting to determine whether Tenascin-C modulates the pro-tumorigenic effects of other integrins, besides alpha2beta1, in glioma.

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Sarkar and colleagues also noticed that treating glioma cell cultures with Tenascin-C increased expression of some Notch pathway components, including the ligand Jagged1, as well as increased production of the NICD (1). Strikingly, knocking-down Jagged1 completely abolished the proliferative response induced by exogenously applied Tenascin-C, although it did not reduce basal cell proliferation (1). This was in line with the observation that high Jagged1 expression levels in human gliomas correlate with a shorter patients' survival (1). Of note, previous studies have demonstrated that administration of soluble Jagged1 promotes clonal colony formation in NSC and glioma stem cell cultures using the neurosphere assay (13,22). Intriguingly, it has been shown that Tenascin-C itself can be a direct target of the canonical Notch pathway in glioma and manipulating Notch modulates Tenascin-C production by the tumor cells (3). Thus, the Notch-Tenascin-Jagged1 axis could establish a positive feedback loop that boosts Notch signaling activity in glioma.

A question that remains open is why treating glioma cells with Tenascin-C induced Jagged1 and NICD, but did not significantly change the expression of canonical Notch targets of the Hes/Hey family (1). Moreover, in some circumstances, high Jagged1 levels can inhibit expression of Hes/Hey genes in glioma cells in cis, potentially though the activity of the Jagged1 intracellular domain (23). Interestingly, the canonical Notch signal can support a relatively slow-cycling state rather than promoting proliferation (12) and even exert a tumor suppressive action in some forms of the disease (17). It would be important to determine if the pro-proliferative effect of Tenascin-C in glioma is mediated by a non-canonical Notch activity such as potentiation of Hypoxia-inducible-factor 1 alpha signaling (24), which could in turn increase Tenascin-C expression (25), and how Notch can promote proliferation versus quiescence of brain tumor cells in a context dependent manner.

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