Glioblastoma is the most common primary brain tumor, comprising 52% of all primary brain tumors. Despite advances in treatment, glioblastoma remains virtually incurable, with a median survival of approximately 15 months. A chief cause of the high mortality of glioblastoma is the invasive nature of the tumor, which renders full resection of tumor cells practically impossible. Thus, understanding the mechanisms that underlie glioblastoma invasion is crucial for developing new treatment approaches for this devastating disease.

In this issue of the Journal, Edwards et al. (1) identify connective tissue growth factor (CTGF) as a secreted factor that stimulates the migration and invasion of glioblastoma cells. They show that CTGF, which is produced at high levels by reactive astrocytes bordering the tumor, binds a complex comprising tyrosine kinase receptor type A (TrkA) and integrin B1 on glioma cells, which leads to the activation of nuclear factor kappa B (NF-κB) signaling. NF-κB signaling activates the zinc finger E-box-binding homeobox 1 (ZEB-1) transcription factor, which transcriptionally represses E-cadherin, thereby enhancing invasion and migration.

CTGF is a potent modulator of intercellular signaling and extracellular matrix function. It has chemotactic and mitogenic activity for fibroblasts and other cells. CTGF expression is induced by many growth factors, and CTGF itself binds directly to bone morphogenetic proteins, transforming growth factor B, and vascular endothelial growth factor (VEGF) and modulates their activities. It stimulates the production of extracellular matrix components such as collagen and fibronectin as well as integrins. CTGF also binds integrins and various matrix components, including heparin, fibronectin, and matrix metalloproteinases, and this binding alters the activities of both extracellular matrix components and CTGF itself (2,3).

CTGF expression is most frequently linked to pathologies associated with inflammation and fibrosis throughout the body. For example, CTGF expression has been implicated in fibrosis of the kidney, liver, lung, pancreas, and skin; in atherosclerosis; and in inflammatory bowel syndromes. Strikingly, CTGF is overexpressed in many cancers that have a substantial fibrotic component, including pancreatic cancer, breast cancer, and melanoma. CTGF expression is also high in sarcomas and chondrosarcomas, which like fibroblasts are of the mesodermal lineage (3,4).

In the brain, elevated CTGF expression has been observed in various cell types, primarily during injury response, inflammation, and reactive gliosis. For example, increased CTGF expression is seen in spinal cord injury, amyotrophic lateral sclerosis, cerebral infarction, brain trauma, and models of excitotoxic brain damage (5,6). Elevated expression of CTGF is well characterized in reactive astrocytes, and CTGF is also expressed in pathological contexts by microglia, fibroblasts, smooth muscle cells, endothelial cells, and neurons (5,7). Not surprisingly, then, altered CTGF expression has been observed in brain tumors as well. Indeed, CTGF is overexpressed in 58% of primary gliomas, and expression is correlated with tumor grade and patient survival independent
of grade (4). In addition, CTGF was detected in a screen for genes expressed by migratory glioma cells, and CTGF knockdown inhibited migration in vitro (8).

The close association between CTGF expression and a variety of inflammatory and injury-response processes as well as cancers with a fibrotic component highlights the broader parallels between inflammation, injury, and cancer. The idea that cancer is a deregulated response to injury is an old one, and chronic inflammation has long been known to be a risk factor for cancer. Injury to the brain triggers a unique response of inflammation and reactive gliosis, sometimes including revascularization via angiogenesis. This response involves the coordinated proliferation, migration, and recruitment of multiple cell types, which is facilitated by extensive intercellular communication. Reactive astrocytes and oligodendrocyte precursor cells proliferate and migrate to the site of injury. Microglia proliferate, migrate, and release inflammatory cytokines that stimulate astrocyte activation and modulate the permeability of the blood–brain barrier. In some cases, endothelial cells and pericytes are stimulated to proliferate and generate new vessels to vascularize injured tissue (9,10).

In many ways, the glioblastoma microenvironment resembles a wound site. Reactive astrocytes surround the tumor border, and activated microglia are found throughout the lesion. The vasculature is hyperproliferative, and the blood–brain barrier is disrupted. The intercellular signaling pathways that regulate inflammation and reactive gliosis are also active in gliomagenesis and the glioblastoma microenvironment. For example, epidermal growth factor is expressed in response to brain injury and activates reactive astrocytes, and epidermal growth factor receptor is one of the most recurrently amplified and mutated genes in glioblastoma (10,11). VEGF expression in the brain after injury promotes vascularization and activates astrocytes, and high levels of VEGF are produced by glioblastomas and drive tumor neovascularization (10,12). Sonic hedgehog is expressed by reactive astrocytes in response to injury and stimulates oligodendrocyte precursor proliferation, and sonic hedgehog signaling is active in a subset of gliomas and needed for tumor growth in glioblastoma models (13,14).

The extensive cell migration seen in glioblastomas is also seen in reactive gliosis, which is characterized by extensive migration of astrocytes, oligodendrocyte precursor cells, and microglia. This cell migration is facilitated by interactions with the extracellular matrix, chemotactic signals, remodeling of the extracellular matrix by matrix metalloproteinases, and modulation of cell–cell contacts (15). It is notable that CTGF, nominally a growth factor, also modifies growth factor activity, matrix composition, and integrin signaling and has now been shown by Edwards et al. (1) to regulate E-cadherin expression. Thus, CTGF modulates nearly all aspects of the signaling that regulates cell migration.

The work by Edwards et al. (1) also identifies ZEB-1 as an important downstream effector of CTGF and NF-κB signaling in glioblastoma. NF-κB signaling is well characterized in cancer and the injury response, whereas ZEB-1 is known transcriptional repressor of E-cadherin. However, activation of ZEB-1 by NF-κB signaling is not well described and has mostly been examined in the context of epithelial to mesenchymal transition (16). The direct transcriptional link between NF-κB and ZEB-1 in glioblastoma, resulting in repression of E-cadherin and enhanced tumor invasion, is novel. Given the parallels between tumorigenesis and the injury response and the importance of CTGF in these processes, it will be interesting to see if ZEB-1 regulation of E-cadherin expression and cell migration is important in injury response and inflammation as well. In fact, one previous study (17) reported a ZEB-1-mediated neuroprotective response to brain ischemia. ZEB-1 has also been implicated in suppression of oncogene-induced senescence (18); however, it remains to be seen whether CTGF signaling and the NF-κB–ZEB-1 link contributes to evasion of senescence in addition to invasion.

The findings of Edwards et al. (1) underscore the importance of the complex relationship between the tumor and its microenvironment, in which tumor cells are frequently able to co-opt normal physiological processes for their own advantage. The identification of CTGF as an agonist of glioma invasion has several potentially useful clinical implications. Delineation of the signaling pathway from CTGF through to decreased expression of E-cadherin may have potential as a biomarker for glioma invasiveness. Finally, the parallels between injury and neoplasia suggest that glioblastoma treatments that limit inflammation may have some effectiveness in extending the survival of glioblastoma patients.

References


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