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A Fyn romance: tumor cell Fyn kinase suppresses the immune microenvironment

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See the article by Comba et al in this issue, pp. 806–818.

So far, single agent immune checkpoint blockade of T cells has failed to improve the lives of patients with glioblastoma (GBM). The story is not over, as there may be an advantage to treatment prior to surgery,[1] and even in the failed trials, there have been patients who had durable responses. But, what about the other cells in the microenvironment? There has been a growing appreciation that myeloid cells also play a pivotal role in enabling glioma cells to thrive.[2–6] One way these cells work is by negatively regulating T cells that might otherwise respond to and attack the tumor. Therefore, understanding what regulates suppressive myeloid cells in the microenvironment may enhance treatment options.

To this end, in this issue, Comba et al investigate the role of Fyn,[7] an Src family non-receptor kinase that is highly expressed in GBM.[8] Fyn tyrosine kinase is downstream of commonly mutated receptor tyrosine kinases in GBM, such as epidermal growth factor receptor (EGFR), platelet derived growth factor receptor (PDGFR), and carbon-11 methionine (c-MET). Fyn activation is best understood for its role in driving Ras-dependent pathways; however, Fyn also activates non-Ras-dependent pathways, and there may be a recursive loop between Ras and Fyn. Consistent with this, Fyn suppression in vitro in glioma cells reduces migration and proliferation. So, it was unexpected when Fyn-suppressed cells implanted into immunocompromised mice still killed mice at the same rate as cells in which Fyn was not perturbed. Why would this be? These mice lacked an adaptive immune system: when the same experiment was done in immunocompetent mice, mice receiving Fyn-suppressed tumor cells lived longer and had a reduction of myeloid-derived suppressor cells in the tumor microenvironment. In vitro stimulation assays also clarified that the myeloid suppressor cells from these mice have a reduction in their inhibitory effect on T cells. There are several categories of myeloid derived suppressor cells; the authors demonstrate that the immunosuppressive function they observe occurs through polymorphonuclear-myeloid derived suppressor cells but not through monocytic ones.

Comba et al should be commended for their detailed investigations, which combine computational tools, transcriptional profiling, a number of genetically engineered mouse glioma models, and functional studies. This work is important because it begins to connect the dots of how a tumor cell may engage its microenvironment to make it more hospitable for growth. Targeting Fyn may help in two ways: reducing tumor cell proliferation and making the immune microenvironment better engage and strike the tumor. An important lesson here is that even though in vitro evidence suggests that Fyn does its job in a cell-intrinsic manner, mouse models and context matter and detailed investigations into tumor cell–microenvironment interactions can be much more illuminating.

In the future, it will be important to test whether these exciting findings hold true for other, non–neuroblastoma-Ras (N-RAS)-driven mouse models of glioma. In addition, following up on the transcriptional findings in this work, it will be useful to identify the factors the Fyn-driven tumor cells use to communicate with the microenvironment. Since Fyn is also expressed in neurons and required for their migration, it will be exciting to explore how neuronal populations in the tumor reshape the immunological response to tumors. In future work, Fyn expression in immune cells themselves will be important to investigate in the setting of GBM. Single cell RNA sequencing analysis of human tumors will help clarify which populations contribute the most to the observed high expression of Fyn in bulk samples. Genetically engineered Fyn knockout mice,[9] which are viable, will be an important tool to further parse the role of Fyn in distinct cell populations. Given a new appreciation for sex differences in GBM outcomes,[10] investigating such differences in the role of Fyn activity will also be a promising avenue for future investigation. In short, Comba and colleagues have laid the foundation for

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understanding how glioma cells entrain the host environment to be suitable for their growth. Putting an end to this communication may lead to new ways to treat GBM.

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