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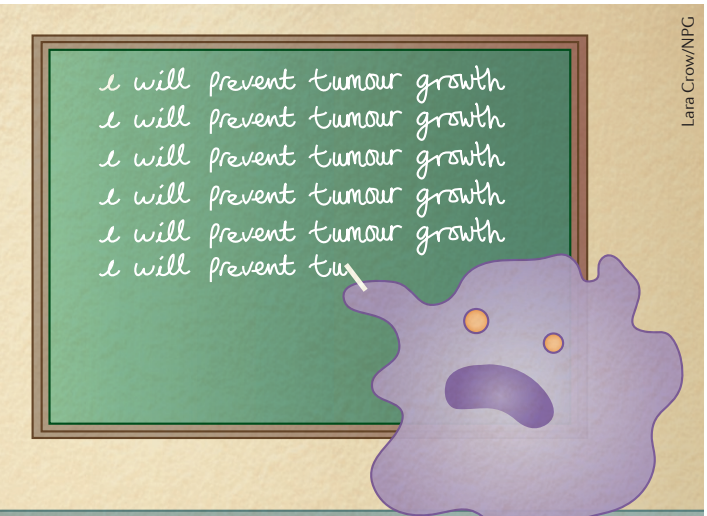

Lara Crow/NPG

TUMOUR MICROENVIRONMENT

Teaching old macrophages new tricks

> CSF1R inhibition reduced the M2 polarization of TAMs

Although the tumour microenvironment is an attractive therapeutic target, implementing strategies that effectively modify this compartment has been challenging. Using several preclinical models, Johanna Joyce and colleagues have found that inhibition of macrophage colony-stimulating factor 1 receptor (CSF1R) can block glioblastoma growth by changing the polarization of tumour-associated macrophages (TAMs) from pro-tumorigenic to antitumorigenic.

Mice expressing platelet-derived growth factor B (PDGFB) in glial progenitor cells (termed PDG mice) develop tumours that are similar to the proneural subtype of human glioblastoma. The tumours in these mice contain increased numbers of CSF1R-expressing TAMs (the presence of which has been associated with poor prognosis and higher grade in human glioblastoma), suggesting that targeting these TAMs might be an effective therapeutic strategy.

The authors treated PDG mice that had small or undetectable tumours with the brain-penetrant CSF1R inhibitor BLZ945; this significantly improved the survival of the mice compared with vehicle treatment. Furthermore, those tumours that did develop in mice treated with BLZ945 were lower grade. BLZ945 treatment of mice with established high-grade tumours also led to tumour regression in most mice. Intracranial xenograft growth of patient-derived tumour spheres or cell lines of human proneural glioblastoma in non-obese diabetic severe combined immunodeficient (NOD–SCID) mice (which have macrophages) was also inhibited by BLZ945.

How does BLZ945 reduce glioblastoma growth? Analysis of tissues from BLZ945-treated PDG mice showed that glioblastoma cell proliferation was reduced and apoptosis was increased, leading to a large decrease in tumour size. Various experiments using cultured cells indicated that BLZ945 did not have any direct effects on the growth of glioblastoma cells, but that it inhibited the growth of wild-type macrophages as expected. However, BLZ945 did not affect the number of TAMs in PDG mice or in the xenograft models. Analyses of conditioned media from PDG tumour cell lines or from human glioblastoma cell lines indicated that TAMs are protected from BLZ945-mediated apoptosis by glioblastoma-derived factors.

To understand how BLZ945 might suppress tumours, the authors turned to microarray gene-expression profiling of TAMs from PDG mice treated with either BLZ945 or vehicle. They identified a gene signature associated with BLZ945 treatment that included the downregulation of several genes that have previously been shown to be associated with pro-tumorigenic M2 macrophages. Expression of these M2 macrophage-associated genes was increased when wild-type macrophages were exposed to conditioned medium from glioblastoma cells, but decreased in the presence of BLZ945. Therefore, CSF1R inhibition reduced the M2 polarization of TAMs. BLZ945 also increased phagocytosis by TAMs, and both this and the change in polarization may have a role in reducing tumour size.

To further understand the effects that TAMs have on glioblastoma cell growth, the authors stimulated wild-type macrophages with glioblastoma-cell-conditioned medium to mimic the glioblastoma microenvironment *in vitro*. Co-culture of the stimulated macrophages with PDG tumour cells increased tumour cell proliferation, which was subsequently blocked by BLZ945. Conditioned medium taken from stimulated macrophages promoted proliferation by the activation of signalling downstream of AKT in the glioblastoma cells. Thus, there seems to be a complex interplay between TAMs and tumour cells.

Does this translate to human tumours? The TAM gene signatures identified by the authors from PDG mice were used to predict survival in human proneural glioblastomas — those patients whose whole tumours had a gene expression signature similar to that from BLZ945-treated TAMs showed better survival than those whose tumours had a gene expression signature representative of M2-polarized TAMs. Whether CSF1R inhibition can be successfully used in patients with proneural glioblastoma to convert TAMs into a tumour-suppressive phenotype, and whether similar strategies can be used to treat other glioblastoma subtypes or other tumour types are important future questions.

Sarah Seton-Rogers

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