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Scarring, without regeneration, is the therapeutic challenge for making palliative glioma treatments curative

A recent study published in *Neuro-Oncology*^[1] shows an increase in pleiotrophin (PTN) expression following glioblastoma resection. This observation adds new evidence of the existence of the tumorigenic side effects of surgical resection.^[2]

PTN, also known as Heparin-Binding Brain Mitogen and Heparin-Binding Growth Associated Molecule, has long been associated with regenerative healing. For example, PTN is a common contributor to the bone, muscle, and liver regeneration.^[3] It also regulates the expansion and regeneration of hematopoietic stem cells.^[4] The elevated level of PTN after tumor resection is, therefore, consistent with a tissue regenerative healing response to surgery injury; that will be the “tumor recurrence.” Any treatment that does not consider this issue is condemned to be palliative, rather than curative.

Contrary to tumor tissues, most adult organs have limited regenerative potential. The endpoint of their healing process is the formation of a scar. In the brain, the glial scar creates the barrier that surrounds and isolates the lesion core. Perivascular and meningeal fibroblasts and pericytes make fibrotic scars that occur within lesion cores. The scarring process is a necessary contributor to brain healing.^[5] The scar is not a consequence but a factor in the healing process. The formation of a mature glial scar takes several weeks to reach completion and requires the absence of exacerbating injury.^[5] The spread of invasive cancer cells and therapy-induced tissue damages are such exacerbating injuries. A largely overlooked point is that although invasive brain tumors elicit reactive gliosis, they are not surrounded by a well-defined astrocyte or fibrotic scar.^[5] The question arises as to why we have neglected to consider the resolution of the scarring process into a mature scar as a therapeutic imperative.

In the words of Hippocrates, “*Medicine consists of adding and subtracting, subtracting what is in excess, adding what is deficient.*” In glioblastoma, the readily observable excess to subtract is the tumor mass. This may have led us to focus our therapeutic efforts on subtractive treatments such as tumor resection and killing cancer cells. To observe a deficiency like a scar defect is less straightforward. A deficiency is defined in reference to a control. Neither scar is observable in patients, nor in the normal nontrauma tissues used as controls in our studies. Scarring is an emergent function of tissues; a cell does not scar, but tissue does. Therefore, the observation of a mature scar is also not common in experimental cell culture studies. Moreover, once observed,

dealing with a deficiency can be tricky. Tumor hypoxia is such an example. Even though hypoxia is a deficiency, we initially designed our anti-angiogenic strategy not to add but to subtract oxygen. As a result, the approach initially failed before we discovered its therapeutic interest to normalize the tumor vasculature, *i.e.*, “*in adding what is deficient.*” Indeed, we could restate Hippocrates’ principle in “*Medicine consists in normalization.*” A critical missing step in our therapeutic strategies is the normalization of the healing process through the formation of its endpoint, the functional scar. It is necessary to resolve this issue to make palliative therapies curative. Scars are borders, and history shows us that the restoration of borders may help to resolve conflicts and prevent invasions.

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Conflicts of interest

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Letter to the Editor

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