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Inflammation to Rebuild a Brain:

Inflammation in the zebrafish brain stimulates neurogenesis and tissue regeneration

Nephi Stella

Department of Pharmacology, University of Washington, 1959 NE Pacific Street, Seattle, WA 98195, USA

Nephi Stella: nstella@u.washington.edu

The overarching strategy of all immunesystems is as predictable as the plot of an episode of *Mission: Impossible*. A short-lived message describing the problem reaches commanding immune cells. A team of specialized expert cells is then dispatched to deal with the problem. Once successfully addressed, the team disappears without leaving a trace. On page 1353 of this issue, Kyritsis *et al.* (1) characterize an astonishing type of immune response—a new team of “executioner” cells—that is implemented when the zebrafish brain is injured. By tricking the immune system into believing neuronal injury had occurred, the authors discovered that inflammation alone is sufficient to switch on neurogenesis. The molecular components used by the highly specialized immune cells that promote neurogenesis represent potential novel therapeutic targets that could promote brain repair.

What type of specialized effector cells (“executioner” cells) are recruited in response to tissue damage, stress, or infection? Immunologists refer to two general characters adopted by these cells: pro- and anti-inflammatory phenotypes, or M1 and M2 phenotypes when referring to macrophages (2). These are distinguished by increased release of free radicals (nitric oxide) or anti-inflammatory cytokines [interleukin-4 (IL-4) and IL-10], respectively. However, macrophages can adopt other phenotypes that cannot be assigned to this simplistic binary fate. For example, those that invade tissue afflicted by neurodegeneration or brain tumors adopt qualities that do not correspond to the classical M1 and M2 definitions (3, 4). This implies that a more complex, multidimensional range of change in macrophage exists, allowing for the recruitment of cells that have more specialized skills than previously recognized.

Microglia, the macrophages of the brain, patrol a privileged environment that dictates their phenotypic diversity and shapes their response to specific types of neuronal damage (5). The brain is isolated from the rest of the body by the so-called “blood-brain barrier,” which protects it from circulating toxins and peripheral immune cells. It was long thought that mammalian microglia adopt an M1 phenotype in response to neuronal damage and produce proinflammatory mediators. It is now known that microglia adopt an M2 phenotype that counterbalances and resolves the preceding M1 response. Still, this dichotomy fails to capture microglia’s true phenotypic diversity. These cells can produce entirely different classes of secreted effector signals, some of which are involved in tissue repair, including growth factors (brain-derived neurotrophic factor, vascular endothelial growth factor, and transforming growth factor- β), immune response modulators (interferon- γ , monocyte chemoattractant protein-1, and C5a), and signaling lipids (prostaglandins and endocannabinoids) (6, 7). Accordingly, microglia phenotype is more plastic than previously thought.

Kyritsis *et al.* show that an archetypal signaling lipid, leukotriene C4 (LTC4), single-handedly promotes regenerative neurogenesis in the zebrafish brain (see the figure). The plethora of lipid signals that are steadily released by both injured cells within affected

tissues and the invading immune cells form a dynamic network of information that fine-tunes and orchestrates the tactics implemented by immune executioner cells in mammals (8). How does this regenerative pathway work in zebrafish, and why doesn't it work in mammals? What other molecular components are involved? Is it necessary for executioner cells to reach a critical mass at the lesion site? If so, cell migration would be a critical feature of this inflammatory response. Kyritsis *et al.* found that production of the secreted protein S100 β by glia in the zebrafish brain increased during this particular response. S100 β promotes neuronal differentiation and survival in response to neuronal injury in the mammalian brain, but may promote a persistent damaging neuroinflammatory state when produced in high amounts (9). This protein is a predictive clinical serum marker of brain injury and increased blood-brain barrier permeability (10). Whether the beneficial and/or detrimental effects of S100 β depend on the type of injury remains an open question.

Kyritsis *et al.* also identified the transcription factor Gata3 in both the immune executioner cells and the neuronal progenitor cells as a likely molecular switch that controls the repair phenotype of the inflammation. Could this switch be targeted by therapeutics to promote neuronal repair? Further studies are needed to establish where the inflammatory repair program diverges between zebrafish and mammals. It may be convenient to think of the point of divergence as positioned upstream or downstream of the zebrafish and mammalian glia cell response. Upstream differences may include the phenotype of respective glia at the site of injury and the types of molecules that they release. Downstream differences may include differences in LTC4 signaling or impaired ability of mammalian neuronal progenitor cells to respond to LTC4.

Mammalian neurogenesis can be turned on in the adult hippocampus, olfactory bulb, and other areas throughout the central nervous system, albeit at lower levels (11). Some mammalian brain injuries are associated with an inflammatory response, an increase in the proliferation of neuronal progenitor cells within the neurogenic areas, and sometimes the migration of these newborn neurons to the sites of injury (6). In humans, the positive correlation between the induction of inflammation and neurogenesis occurs during acute injuries induced by ischemia and epilepsy, and also in certain neurodegenerative diseases, such as Parkinson's disease and amyotrophic lateral sclerosis, although with much lower incidence. Perhaps some of these immune functions are deregulated in the brain and peripheral tissue of patients with neurodegenerative diseases (4) and thereby contribute to the development of slow-progressing neurodegeneration.

There is clear strength in combining genetics and pharmacology in a model organism to study the complex cellular interactions implemented by the immune system. Our mission (should we choose to accept it) is to validate these findings in the mammalian brain and to search for new therapeutic venues that will control this particular arm of the immune system to swiftly temper and repair neuronal injuries and slowly progressing chronic neurodegeneration.

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Figure 1. Brain regeneration

In the zebrafish brain, injured neurons release a signal (LTC₄) that stimulates resident immune cells (microglia, leukocytes, and other glia) to release a signal (LTC₄) that promotes neurogenesis. The transcription factor Gata3 in both the immune cells and the neuronal progenitor cells may operate as a molecular switch that controls the repair phenotype of the inflammation.