Vision Restoration with Granulocyte Colony-Stimulating Factor Following Traumatic Injury

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PUBLIC ABSTRACT

Explosive devices have become the preferred weapon in the majority of terrorist attacks in war zones. A recent report documented that 78% of military personnel wounded in action and treated at medical units in Iraq had been injured by explosive devices. Although more obvious penetrating injuries are quickly diagnosed and treated, there is also tissue damage resulting from increased pressure during the blast wave. This was recognized initially in high air capacity tissues such as lung, auditory system, and gastrointestinal tract, but it is now clear that blast over pressure (BOP) leads to traumatic brain injury (TBI) and retinal damage causing loss of vision. Indeed, a sentinel study published in 2011 revealed that 20% of military personnel injured by explosion exhibited signs of eye trauma and vision defects. These effects are chronic and progressive, appearing several weeks after blast injury and persisting. Photoreceptors in the retina convert light into electrical signals that are transmitted to the brain for vision. They are perhaps the most specialized cells in the body, and they are sensitive to environmental stresses such as light overexposure, retinal detachment, and drugs such as iodate used to target the thyroid, as well as genetic mutations that cause retinal stress. These environmental stresses, including BOP, and the stress resulting from genetic mutations in the retina activate a common pathway that causes inflammation and photoreceptor death. Moreover, this same inflammatory pathway appears to extend beyond the retina to cause neuronal death in TBI and spinal cord injury. Following death of photoreceptors and neurons in the brain and spinal cord, specialized scars form. In the retina, these scars arise from Muller glial cells, and this gliotic scarring poses a major barrier to attempts to restore photoreceptor number and function by stem cell transplantation. Unfortunately, gliosis is not prevented or reversed by traditional anti-inflammatory treatments. In summary, BOP can be grouped with a variety of other environmental factors, as well as genetic mutations, in activation of a common pathway that is detrimental to the repair of retinal photoreceptors but also neurons in injured brain and spinal cord. Thus, if one can characterize and block this pathway, then the results would have far-reaching implications for multiple common central nervous system-related battlefield injuries. But to date, there has been little success in either blocking gliotic scarring or restoring functional photoreceptors or other neurons in damaged brain and spinal cord.

Although photoreceptors are slowly replaced during normal tissue maintenance, this replacement pathway is overwhelmed and cannot replace the cells when there is extensive damage. But, photoreceptor regeneration is classically seen in fish and amphibians and is also evident in a limited fashion in neonatal mice. The source of these new photoreceptors is Muller glia. Paradoxically, as noted above, these cells are also the cause of glial scarring. Thus, the gliotic scarring pathway, which acts as a major barrier for tissue repair, and this photoreceptor regeneration pathway are mutually exclusive in Muller cells. Therefore, directing Muller cells toward such a photoreceptor regeneration pathway might have the added benefit of preventing scarring. Surprisingly, recent studies show that human Muller cells in culture can efficiently generate photoreceptors, raising the possibility that a latent Muller cell regeneration pathway might be inducible in
mammals.

In lower vertebrates, a signaling pathway known as Jak/Stat mediates the replacement of photoreceptors, as well as neurons in damaged spinal cord. Jak/Stat3 can be activated by a family of factors that bind to receptors on the surface of cells. This binding transmits a signal to reprogram the Muller cells to photoreceptor progenitors (while simultaneously blocking the gliotic scarring pathway). Interestingly, one member of the family of factors that activates Jak/Stat is granulocyte colony-stimulating factor (G-csf). G-csf (Neupogen) is a Food and Drug Administration (FDA)-approved drug that is routinely utilized to boost expansion and differentiation of bone marrow stem cells depleted in chemotherapy patients. Here, we demonstrate that Gcsf can act on Muller cells in vivo to switch the cells from their gliotic scarring pathway to a photoreceptor regeneration pathway. We propose to study an off-target function for G-csf in boosting photoreceptor replacement and preventing gliotic scarring in a rat model of BOP. Because G-csf is already FDA-approved and widely utilized clinically, the timeline for its translation to clinical use would be rapid.