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BRAIN RESEARCH REVIEWS

Review

Olfactory ensheathing glia: Their contribution to primary olfactory nervous system regeneration and their regenerative potential following transplantation into the injured spinal cord

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ABSTRACT

Olfactory ensheathing glia (OEG) are a specialized type of glia that guide primary olfactory axons from the neuroepithelium in the nasal cavity to the brain. The primary olfactory system is able to regenerate after a lesion and OEG contribute to this process by providing a growth-supportive environment for newly formed axons. In the spinal cord, axons are not able to restore connections after an injury. The effects of OEG transplants on the regeneration of the injured spinal cord have been studied for over a decade. To date, of all the studies using only OEG as a transplant, 41 showed positive effects, while 13 studies showed limited or no effects. There are several contradictory reports on the migratory and axon growth-supporting properties of transplanted OEG. Hence, the regenerative potential of OEG has become the subject of intense discussion. In this review, we first provide an overview of the molecular and cellular characteristics of OEG in their natural environment, the primary olfactory nervous system. Second, their potential to stimulate regeneration in the injured spinal cord is discussed. OEG influence scar formation by their ability to interact with astrocytes, they are able to remyelinate axons and promote angiogenesis. The ability of OEG to interact with scar tissue cells is an important difference with Schwann cells and may be a unique characteristic of OEG. Because of these effects after transplantation and because of their role in primary olfactory system regeneration, the OEG can be considered as a source of neuroregeneration-promoting molecules. To identify these molecules, more insight into the molecular biology of OEG is required. We believe that genome-wide gene expression studies of OEG in their native environment, in culture and after transplantation will ultimately reveal unique combinations of molecules involved in the regeneration-promoting potential of OEG.

Contents

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1. Introduction

The primary olfactory nervous system has the remarkable capacity to continuously form new primary olfactory neurons during adulthood (Farbman, 1992; Graziadei and Graziadei, 1979b). The direct exposure of primary olfactory neurons to the external environment makes them more susceptible to chemical or traumatic injury. The ability to form new neurons from a compartment of stem cells has apparently been maintained in mammals, since many mammalian species are dependent on the sensory perception of smell to survive. Olfactory neurogenesis takes place in the basal cell layer of the olfactory epithelium (Graziadei and Graziadei, 1979b). After an injury to the primary olfactory system, neurogenesis is enhanced (Graziadei and Graziadei, 1979a). New primary olfactory neurons grow axons to the olfactory bulb and establish novel functional connections (Costanzo, 1985; Doucette et al., 1983; Harding et al., 1977; Monti Graziadei et al., 1980). These axons grow along specialized glial cells, the OEG, which are found throughout the primary olfactory pathway from the lamina propria to the olfactory bulb (Doucette, 1990). The mammalian primary olfactory system is the only neural tissue where axons are capable to grow directly into the central nervous system (CNS) throughout adulthood (Doucette, 1991; Raisman, 1985).

In contrast to the vigorous neurogenesis and axonal growth that occurs following lesions of the mature primary olfactory system, injury to the CNS and in particular, the spinal cord, results in permanent loss of neuronal connectivity. One way to study the underlying mechanisms of successful regeneration is to investigate the molecular and cellular processes that are responsible for the remarkable regeneration in the primary olfactory system. An important factor that determines the regenerative potential of the olfactory system is the presence of OEG. OEG play an important role in the growth and guidance of primary olfactory axons towards the olfactory bulb (Doucette, 1990, 1991; Raisman, 1985). These properties of OEG have inspired studies on the potential of OEG to stimulate regeneration of injured spinal cord pathways. Although the first transplantation studies reported very promising results, several studies now conclude that the effects of OEG have probably initially been overrated (Lu et al., 2006; Pearse et al., 2007; Steward et al., 2006).

Here, we give an overview of the cellular and molecular characteristics of neuroregeneration in the primary olfactory system with an emphasis on the role of OEG. Furthermore, the regeneration-promoting potential of OEG after implantation will be discussed. They are able to survive in the spinal cord and integrate in neural scar tissue. The latter property appears to be a clear difference between OEG and Schwann cells (SCs), glia cells also originating from a regenerative nervous system, the peripheral nervous system (PNS). In the future, a genome-wide comparison of differences in gene expression between OEG and SCs should reveal the unique molecular properties of these two glia cells. The functional validation of these molecular differences will be essential to ultimately create a glia cell with novel and improved regeneration-promoting properties.

2. Anatomy of the primary olfactory system and cellular origin of its neurogenic potential

Primary olfactory neurons are located in the mucosa in the nasal cavity. Primary olfactory neurons project axons to the olfactory bulb situated at the rostral side of the brain within the cranium (Fig. 1A). The mucosa is overlying the nasal septum and turbinates and consists of the neuroepithelium and the lamina propria. The lamina propria is a connective tissue and is separated from the epithelium by a basal lamina (Farbman, 1992). The epithelium contains different cell types, including primary olfactory neurons, basal cells, supporting or sustentacular cells and flat cells forming the ducts of the Bowman's glands, which themselves lie in the lamina propria (Farbman, 1992; Graziadei and Graziadei, 1979b) (Fig. 1B).

Mature primary olfactory neurons are bipolar cells located in the intermediate zone between the apical and basal sides of the epithelium. At the apical side, the dendrite projects a set of cilia into the mucus, where the actual detection of odorants takes place. The dendrites of olfactory neurons are separated from each other by the sustentacular cells, which contact the basal lamina by long cytoplasmic processes. Sustentacular cells are thought to play a role in detoxification (Hadley and Dahl, 1982) and in phagocytosis of degenerating primary olfactory neurons (Suzuki et al., 1996). At the basal side, an axon projects into the lamina propria, where it forms bundles with other axons that converge into larger nerve fascicles. Once axons have entered the lamina propria, they are enwrapped by OEG, which guide them through the cribriform plate to the olfactory bulb. Nerves