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Review

Understanding the neural repair-promoting properties of olfactory ensheathing cells

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ABSTRACT

Olfactory ensheathing glial cells (OECs) are a specialized type of glia that form a continuously aligned cellular pathway that actively supports unprecedented regeneration of primary olfactory axons from the periphery into the central nervous system. Implantation of OECs stimulates neural repair in experimental models of spinal cord, brain and peripheral nerve injury and delays disease progression in animal models for neurodegenerative diseases like amyotrophic lateral sclerosis. OECs implanted in the injured spinal cord display a plethora of pro-regenerative effects; they promote axonal regeneration, reorganize the glial scar, remyelinate axons, stimulate blood vessel formation, have phagocytic properties and modulate the immune response. Recently genome wide transcriptional profiling and proteomics analysis combined with classical or larger scale "medium-throughput" bioassays have provided novel insights into the molecular mechanism that endow OECs with their pro-regenerative properties. Here we review these studies and show that the gaps that existed in our understanding of the molecular basis of the reparative properties of OECs are narrowing. OECs express functionally connected sets of genes that can be linked to at least 10 distinct processes directly relevant to neural repair. The data indicate that OECs exhibit a range of synergistic cellular activities, including active and passive stimulation of axon regeneration (by secretion of growth factors, axon guidance molecules and basement membrane components) and critical aspects of tissue repair (by structural remodeling and support, modulation of the immune system, enhancement of neurotrophic and antigenic stimuli and by metabolizing toxic macromolecules). Future experimentation will have to further explore the newly acquired knowledge to enhance the therapeutic potential of OECs.

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Contents

Abbreviations: ADAMTS1, ADAM metallopeptidase with thrombospondin type 1 motif, 1; ATP, adenosine triphosphate; APP, amyloid beta precursor protein; ANGPT2, angiopoietin 2; Ara-C, arabinosylcytosine; GBA, beta-glucocerebrosidase; BDNF, brain derived neurotrophic factor; L1CAM, cell adhesion molecule L1; CNTFRalpha, ciliary neurotrophic factor receptor; CNTF, ciliary neurotrophic growth factor; COX-2, cyclo-oxygenase-2; CYR61, cysteine-rich, angiogenic inducer; ENTPD2, ectonucleoside triphosphate diphosphohydrolase 2; ESM1, endothelial cell-specific molecule 1; EGFR, epidermal growth factor; FGF2, fibroblast growth factor 2; CX3CL1, fractalkine; FZD1, frizzled class receptor 1; GAL-C, galactosylceramidase; GFRA1, glial cell line derived neurotrophic factor family receptor alpha 1; GFAP, glial fibrillary acidic protein; GDNF, glial-derived neurotrophic factor; GRO, growth-regulated oncogene; IL6, interleukin-6; LEPRE1, leprecan; LIPR, leukemia inhibitory factor receptor; LPL, lipoprotein lipase; P75/NGFR, low affinity nerve growth factor receptor; MBP, myelin basic protein; MMP2, matrix metalloproteinase 2; MSLN, mesothelin; MAP, microtubule-associated protein; CDH2, N-cadherin; NGF, nerve growth factor; NEFL, neurofilament, light polypeptide; NCAM1, neuronal cell adhesion molecule 1; NRP1, neuropilin 1; NT4/5, neurotrophin 4/5; NID2, nidogen 2; NFKB, nuclear factor KappaB; SERPINE1, plasminogen activator inhibitor-1; ON, olfactory nerve; ONF, olfactory nerve fibroblast; PAMP, pathogen-associated molecular pattern; PAR1, proteinase-activated receptor-1; P2X, purinergic receptor P2X, ligand-gated ion channel; P2Y, purinergic receptor P2Y, G-protein coupled; RHOA, ras homolog family member A; RARA, retinoic acid receptor, alpha; ROCK, Rho-associated protein kinase; RND1, Rho family GTPase 1; S100, S100 calcium binding protein; SCARB2, scavenger receptor class B, member 2; SPARC, secreted protein acidic rich in cysteine; SEMA, semaphorin; SMAD7, SMAD family member 7; THBD, thrombomodulin; TIMP2, TIMP metallopeptidase inhibitor 2; PLAT/tPA, tissue-type plasminogen activator; TGF, transforming growth factor; TNF, tumor necrosis factor alpha; TNFRSF1A, tumor necrosis factor receptor superfamily, member 1A; TH, tyrosine hydroxylase; VEGF, vascular endothelial growth factor; VAV1, vav 1 guanine nucleotide exchange factor.

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Introduction

Historical perspective on OEC: from discovery to therapy

The discovery of olfactory ensheathing cells

The profound regenerative capacity of the mammalian primary olfactory system is unique. After damage to the neurons in the olfactory neuroepithelium or to the primary olfactory nerve fibers that form the olfactory nerve new primary olfactory neurons are generated from basal cells in the olfactory epithelium (Graziadei and Graziadei, 1979). The axons of these newly formed neurons grow through the lamina propria into the olfactory nerve layer (ONL) of the olfactory bulb and make new synaptic contacts in the glomeruli on dendrites of mitral, tufted and juxtaglomerular cells (Costanzo, 1985; Doucette et al., 1983; Farbman, 1992; Harding et al., 1977). When nerves from the periphery enter the central nervous system, the PNS–CNS transition zone is normally marked by astrocytes that form the glia limitans (Doucette, 1991). In 1991 it was discovered that the olfactory nerve differs from other nerves that enter the CNS in that this transition zone contains a specialized type of glial cell, the olfactory ensheathing glial cell (OEC) which originate from the neural crest (Barraud et al., 2010; Doucette, 1991). After a lesion, OECs guide the olfactory axons of the newly formed olfactory neurons through the lamina propria towards the ONL and into the glomeruli where they reinnervate their target cells (Doucette, 1990, 1991; Raisman, 1985). Thus OECs form a continuously aligned cellular substrate or pathway that actively supports regeneration of primary olfactory axons from the periphery into the CNS (Li et al., 2005b, 2012). In this review we will refer to OECs derived from the ONL of the olfactory bulb as OB-OECs and OECs derived from the lamina propria as LP-OECs when appropriate. Although these two cell types have many properties in common, some important cellular and molecular differences have been noted (Table 1). If we use the abbreviation OEC the text refers to both subtypes of OECs.

Implantation of OECs in spinal cord lesion paradigms

The unique anatomical position and function of OECs in the primary olfactory system prompted Ramon-Cueto and Nieto-Sampedro in 1994 to purify these cells and to examine their regenerative properties as cell implants after rhizotomy of the dorsal root in rats. Implanted OECs, derived from the adult olfactory bulb (OB-OECs), stimulated regeneration of injured dorsal root ganglion axons into the spinal cord in all eight experimental animals, while in contrast, no axonal growth beyond the lesion was found in the spinal cords of any of the control animals (Ramon-Cueto and Nieto-Sampedro, 1994). In the following years, a large number of studies demonstrated that OB-OEC and LP-OEC implants do promote axonal regeneration after various spinal cord lesions (Franssen et al., 2007; Li et al., 1997; Raisman, 2007; Ramon-Cueto, 2011; Ramon-Cueto et al., 2000; Richter and Roskams, 2008; Ruitenberg and Vukovic, 2008; Tetzlaff et al., 2011; Toft et al., 2013), including a chronic spinal cord lesion (Munoz-Quiles et al., 2009). Implanted OECs not only promote axonal regeneration in the lesioned spinal cord and brain, but these cells also promote functional reconnection of injured axons (Takeoka et al., 2011; Ziegler et al., 2011) remyelinate axons, stimulate blood vessel formation, reorganize the glial scar, have phagocytic properties and modulate the immune response (Barbour et al., 2013; Franklin et al., 1996; Imaizumi et al., 2000a; Li et al., 1997, 2005b, 2012; Plant et al., 2011; Raisman et al., 2012; Ramer et al., 2004; Ramon-Cueto et al., 1998; Roet et al., 2011; Smale et al., 1996; Wewetzer et al., 2005).

OECs also have beneficial effects in other nervous system injuries or diseases

In the last decade, an increasing number of studies have reported improved functional recovery and/or fiber tract regeneration following implantation of OECs in a variety of animal models for neurodegenerative diseases and non-spinal cord pathologies, including amyotrophic lateral sclerosis (ALS), Parkinson's disease and stroke. Here we briefly highlight some of these findings. Firstly, adult OB-OECs improved functional recovery in rodent models for Parkinson's disease when co-transplanted with dopaminergic cells (Agrawal et al., 2004; Johansson et al., 2005; Shukla et al., 2009). Secondly, postnatal OB-OECs promoted survival of rats in a rat model for ALS through neuroprotection and remyelination (Li et al., 2011, 2013). Thirdly, adult OB-OECs enhanced recovery of learning and memory in a rat model for cognitive dysfunction (Srivastava et al., 2009). In this study OECs were implanted with neural progenitor cells in the lesioned hippocampus where they apparently provided neurotrophic support. Fourthly, human derived LP-OECs mixed with olfactory fibroblasts promoted neural plasticity and decreased neurological deficits in murine models for stroke (Shyu et al., 2008). Moreover, postnatal OB-OECs increased myelination and reduced infarct size in a rat model for stroke (Shi et al., 2010; Shyu et al., 2008). Finally, both LP- and OB-OECs improved functional laryngeal reinnervation (de Corgnol et al., 2011; Paviot et al., 2011) and OB-OECs stimulated regeneration of adult rat optic nerve and sciatic nerve axons after a lesion (Guerout et al., 2011; Li et al., 2003; You et al., 2011). Taken together, following transplantation in various peripheral

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