Paracrine factors for neurodegenerative disorders: special emphasis on Parkinson’s disease

The progressive loss of dopaminergic neurons in the ventral mesencephalon is the main pathological hallmark of Parkinson’s disease (PD). Drugs currently available only alleviate the principal symptomatic motor-related disturbances and their benefit is counteracted by side effects in the long time. While cell replacement strategies for approaching PD by means of intrastriatal implantation of dopaminergic neurons showed some encouraging results in a number of patients this therapeutic approach aims primarily to replenish the lack of dopamine but not halting disease progression. Hence, over the past decades various strategies have been exploited to protect the dopaminergic neurons in the ventral mesencephalon from dying. Of special importance are in this context neurotrophic factors, drugs striving against oxidative stress and bioenergetic supplements. Particularly, several neurotrophic factors have been described to specifically increase the survival and/or growth of dopaminergic neurons in vitro and in vivo including neurotrophins and glial cell line-derived neurotrophic factor (GDNF) family members.

The use of stem cells for tissue regeneration elicited hope for the development of better treatment options for many neuropathological conditions. Indeed, in the last decade a considerable number of studies have been conducted to explore the potential of progenitor and stem cells. Importantly to note, in experimental stroke models significant improvement of symptoms was observed, however, histological analysis of some tyrosine hydroxylase (TH; in red) positive neurons (inserts, boxed area in B). Scale bars: 50 μm.

Figure 1 Schematic drawing of the major components in the secretome produced and released by various stem and progenitor cells.

Stem and progenitor cells produce a variety of factors that affect different functions of the targeted neurons. These bioactive proteins or lipids are either released free or in microvesicles and exosomes. Importantly, microRNA and organelles like mitochondria are part of the secretome.

Figure 2 Photomicrographs of human midbrain cell cultures.

The human midbrain (ReNcell-VM) cell line was grown for 1 week in control medium (A) or exposed to endothelial progenitor cells (EPC)-derived conditioned medium (B). The cultures were then immunocytochemically stained for the neuronal marker beta-III-tubulin (in green) and the nuclear marker dapi (in blue). Note the higher fiber network of neuronal cells in the EPC-derived conditioned medium treated cultures. Moreover, EPC-derived conditioned medium administration induced a dopaminergic phenotype as demonstrated by the presence of some tyrosine hydroxylase (TH; in red) positive neurons (inserts, boxed area in B). Scale bars: 50 μm.
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various pro- and anti-inflammatory molecules. These include not only cytokines but also lipids as sphingosine-1-phosphate (SIP) and prostaglandins and also metabolizing enzymes. Importantly, alterations in the SIP signalling have been associated to the pathogenesis of AD while SIP administration has demonstrated neuroprotective effects on experimental models of AD and PD (Pyszek and Strosznajder, 2014).

Nucleotides and nucleosides constitute an important group of paracrine messengers involved in cell growth/differentiation and immune-mediated inflammatory responses. Moreover, it has been proposed that extracellular purines might be considered a valuable tool to promote neuronal tissue homeostasis and repair (Cavaliere et al., 2015). Furthermore, MSC and endothelial progenitor cells (EPC) secerotmes are rich of ECM elements like heparan or chondroitin sulfate proteoglycans as well as metalloproteinases. In addition to the essential role in growth factor signaling and synaptic transmission, ECM directly modulates plasticity. Hence, a number of proteins, as for example SPARC and CRY1 that bind to ECM, are important regulators of cellular functions (Strada et al., 2009); these so called matrix molecules are important constituents of the MSC secretome. It is thus not surprising that an altered ECM composition is involved in the development of neurodegenerative disorders including AD, PD, and schizophrenia. It is now well established that exosomes can exert cytoprotective effects. This phenomenon has been observed also for dopaminergic cells incubated with exosomes derived from MSC (Fjarmalaviaite et al., 2015). A growing amount of observations have shown that the genetic transfer through miRNAs and/or miRNAs carried by microvesicles and exosomes is a crucial element in cell-to-cell communication and instructs both degenerative and reparative processes. The list of miRNA shuttled by the vesicles according to the cells of origin and the disease state is continuously expanding and represents an extraordinary biological tool to harness tissue repair (Smith et al., 2015). It is clear that the effects exerted by secretomes are likely the result of a interplay of multiple factors with a different biochemical nature including proteins, lipids, and nucleic acids, activating different downstream events at the cellular level. Due to the heterogeneous mode of action and assorted composition, predictions of targeted cell populations are challenging. Nevertheless, given that many of the factors present in the secretomes are finally dependent on their specific receptors to be operative multireceptor mapping may offer a novel tool for the identification of such targets.

Studies from our laboratory have shown that the secretome derived from EPC promotes angiogenesis, resistance against oxidative stress in endothelial cells but also the diff-erentiation of neuronal stem/progenitor cells. Importantly to note in the context of PD, is the potential of EPC-derived CM to induce a dopaminergic phenotype in neurons of midbrain cultures (Figure 2). These effects which are mediated by proteaceous and lipid factors are paradigmatic of pleiotropic actions of the secretome (Di Santo et al., 2016).

The use of secretome originated from different cell types is emerging in the field of tissue repair/regeneration due in part to advantages over cell transplantation. Notably, secretome-based therapies pose few concerns with regards to immunogenic reactions and oncogenicity. These features offer the advantage of an allogenic and off the shelf use. Thus, in consideration of the high scalability and the possible, countless modifications, secretomes can be considered an ideal interface between cell-based therapies and conventional drugs. It is, however, important to note that secretome-based approaches have also limitations and drawbacks. In addition to beneficial effects, the variety of active factors that can be found in secretomes can promote tissue fibrosis or even elicit inflammatory responses. Moreover, it has been reported that secretomes derived from senescent cells can in turn propagate senescence in neighbor cells; a phenomenon termed senescence associated secretory phenotype (Zullo et al., 2015).

In sum, the detailed characterization of the different secretomes including mechanisms of action will be an important topic for the full exploitation of their tissue regenerative potentials. Thus, new studies are needed to overcome the current limitations of secretome-based treatments and to achieve alternative and/or complementary therapeutic tools for neurodegenerative disorders.

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