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 revealed that only a small portion of transplanted cells differentiated into mature neurons. Hence, the concept that these cells exert therapeutic actions by replacing defective cells by differentiating into multiple cell types has been gradually revised. It is now believed that the restorative effects observed in cell transplantation settings mainly rely on autocrine/paracrine activities (Andres et al., 2011). In line with this notion, improved tissue functionality is typically associated with low levels of cell engraftment and cell trans-differentiation (Drago et al., 2013). There is a general consensus that the trophic and immunomodulatory paracrine activities are not simple bystander but rather main players of tissue regeneration supported by progenitor/stem cells. Hence, in the present perspective we communicate on the composition and mechanisms of action of the factors secreted by stem/progenitor cells commonly defined as secretome (Liang et al., 2014).

The big variety of active elements released by cells can be tentatively classified in soluble factors and particulates. Classical growth factors and cytokines quantitatively predominate in the group of soluble factors that includes also lipids, extracellular matrix (ECM) components and nucleotides. Importantly to note, ECM components play an important role in juxtacrine signaling, however, in the present study we focus on its role in the secretome of stem/progenitor cells. The category of particulate factors is fundamentally composed of vesicular bodies, which are further distinguished in exosomes and exosomes. Thereby, exosomes range from 100 to 500 nm in diameter. Microvesicles arise from budding of the plasma membrane of a cell and their size range between 100 nm and 1,000 nm. Conversely, exosomes originate from an exocytosis process and are 30 nm to 100 nm sized (Anthony and Shiels, 2013). Microvesicles are important signaling mediators functioning as cargoes of variety of bioactive materials including genetic material (mRNA, microRNA, rRNA, and tRNA) and lipids (Choi et al., 2013). Interestingly, they can also shuttle mitochondria from one cell to the other (Spees et al., 2006). The importance of these particulates is highlighted by the fact that the portion of secreted proteins actually present both in microvesicles and exosomes may reach up 40% (Zullo et al., 2015) (Figure 1). Hence, it is important to note that a big variety of soluble factors and particulates are present in the secretome of stem/progenitor cells.

Most of the current knowledge on the importance of soluble factors for preventing degeneration and promoting recovery has been gathered in studies using mesenchymal stem cells (MSC). Different studies have provided indirect evidence that MSC mediate enhanced survival of nigral dopaminergic neurons and functional recovery in a parkinsonian model of rats by means of secreted factors (Wang et al., 2010). Additionally, the use of conditioned medium (CM) has been found to be secreted by MSC do not rely solely on the trophic and anti-apoptotic functions of neurotrophic factors. It is in fact recognized that the chemotactic stromal cell-derived factor-1 a secreted by MSC promote endogenous repair through the activation of resident neuronal stem cells (NSC) (Wang et al., 2010). Moreover, stimulation of vascular growth by released soluble angiogenic factors is another relevant mechanism for the repair of ischemic tissues, but also for ameliorating the progression of tissue degeneration in Alzheimer’s disease (AD) and PD. Furthermore, the capacity to modulate the inflammation by paracrine factors is of utmost importance to steer neuronal tissues towards damage or repair for all neurodegenerative conditions. In this respect, MSC secrete...
This research was supported by the HANELA Foundation and the Swiss National Science Foundation, No. 31003A_135565 and 406340_128124.

Stefano Di Santo, Hans Rudolf Widmer
Department of Neurosurgery, Neurocenter and Regenerative Neuroscience Cluster, University Hospital Bern, Switzerland University of Bern, Inselspital, CH-3010 Bern, Switzerland

*Correspondence to: Hans Rudolf Widmer, Ph.D., hanswi@insel.ch.
Accepted: 2016-03-10
orcid: 0000-0002-4032-9995 (Hans Rudolf Widmer)
doi: 10.4103/1657-5374.180739


References


