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Review

Potential therapeutic roles of stem cells in ischemia-reperfusion injury

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ABSTRACT

Ischemia-reperfusion injury (I/RI), produced by an initial interruption of organ blood flow and its subsequent restoration, contributes significantly to the pathophysiologies of stroke, myocardial infarction, renal I/RI, intestinal I/RI and liver I/RI, which are major causes of disability (including transplant failure) and even mortality. While the restoration of blood flow is required to restore oxygen and nutrient requirements, reperfusion often triggers local and systemic inflammatory responses and subsequently elevate the ischemic insult where the duration of ischemia determines the magnitude of I/RI damage. I/RI increases vascular leakage, changes transcriptional and cell death programs, drives leukocyte entrapment and inflammation and oxidative stress in tissues. Therapeutic approaches which reduce complications associated with I/RI are desperately needed to address the clinical and economic burden created by I/RI. Stem cells (SC) represent ubiquitous and uncommitted cell populations with the ability to self-renew and differentiate into one or more developmental 'fates'. Like immune cells, stem cells can home to and penetrate I/R-injured tissues, where they can differentiate into target tissues and induce trophic paracrine signaling which suppress injury and maintain tissue functions perturbed by ischemia-reperfusion. This review article summarizes the present use and possible protective mechanisms underlying stem cell protection in diverse forms of ischemia-reperfusion.

Introduction

Ischemia-reperfusion is a state of pathophysiologic stress produced by an initial obstruction of blood flow to organ followed by subsequent perfusion at some later time. The magnitude and duration of ischemia determines the extent of cell dysfunction and/or death. Although reperfusion is required to restore oxygen and nutrient requirements of the tissues, it also results in the exaggeration of local and systemic inflammatory responses which often intensify tissue injury; this phenomenon is known as 'ischemia reperfusion injury or 'I/RI' (Eltzschig and Collard, 2004; Kalogeris et al., 2012, 2016). I/RI is multifaceted and exhibits progressive increases in vascular leakage, transcriptional changes and activation of cell death programs, leukocyte entrapment and inflammation and oxidative stress (Eltzschig and Eckle, 2011). I/RI can be caused by any situation which can compromise the blood supply to an organ. Some of these events can include vascular thrombosis, atherosclerosis, arterial hypotension, organ transplant, aortic cross-clamping, cardiopulmonary bypass, sleep apnea and sickle cell disease (Eltzschig and Collard, 2004; Eltzschig and Eckle, 2011; Kerrigan and Stotland, 1993).

Different organs exhibit different levels of susceptibility to ischemia with the brain being perhaps the most I/RI sensitive organ; irreversible brain damage can become evident within 20 minutes of ischemia (Ordy et al., 1993). This high I/RI sensitivity reflects two major factors: first, the brain has the highest metabolic requirements of any organ and consequently high demands for oxygen and nutrition (Silver and Erecinska, 1998). Secondly, the brain has lower levels of anti-oxidants, e.g. superoxide dismutase, catalase, glutathione peroxidase (Kalogeris et al., 2012, 2016) and heme-oxygenase-1 (Damle et al., 2009), compared to the heart, liver, lungs or kidneys. By comparison, the heart is the second most susceptible organ with irreversible damage occurring after only 20 minutes (Jennings, 1969) followed by the kidney, where organ damage can often occur with 30 minutes of ischemia (Porpiglia et al., 2007). After these, the next major organ influenced by ischemia is the intestine. However, it is often difficult to determine a "point of no return" in intestinal I/RI as initial symptoms of intestine I/RI are often difficult to detect. If intestinal ischemia is detected and treated within 24 hours, the survival rate for mesenteric I/RI is 50%, however, if it is detected later, the survival rate drops to 30% (Kalogeris et al., 2012, 2016).

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Oxidative stress is an important facet of I/RI, and I/RI-associated oxidants are produced by several different enzyme systems including xanthine oxidase, NADPH oxidase (NOX), uncoupled endothelial nitric oxide synthase (eNOS) and electron 'leaking' from the mitochondrial transport chain (Kalogeris et al., 2012, 2016) (Wu et al., 2018). Oxidative stress mainly reflects the evolution of toxic oxidants including superoxide anion radical (O_2^-), hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), and hydroxyl anion (OH^-) (Eltzschig and Collard, 2004) (Kerrigan and Stotland, 1993). The neutrophil "respiratory burst" is one of the main sources of I/RI oxidants which mainly reflects the release of O_2^-derived from NADPH oxidase (Fantone and Ward, 1982) (Kerrigan and Stotland, 1993). Xanthine dehydrogenase is a membrane-associated enzyme which converts hypoxanthine to xanthine and uses NAD^+ as an electron acceptor. However, under ischemic condition it is converted by proteolysis to xanthine oxidase which uses O_2 molecules as electron acceptors, thereby leading to accumulation of hypoxanthine. Upon reperfusion, xanthine oxidase reacts converts hypoxanthine to xanthine forming both superoxide and hydrogen peroxide in the presence of oxygen and catalase (Lee et al., 2014) (Wu et al., 2018). These I/RI evolved ROS help to drive cytokine production (Naik and Dixit, 2011) by activating oxidant sensitive transcription factors like nuclear factor kappa B (NF-κB) (Asehnoune et al., 2004), induction of arachidonic acid and leukotriene B_4 synthesis, increasing expression of cell adhesion molecules e.g. P-selectin, intercellular adhesion molecule (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (Lee et al., 2007) (Carden and Granger, 2000) creating persistently inflammatory environment (Eltzschig and Collard, 2004; Wu et al., 2018). NOX expression and activity are increased during ischemia-reperfusion injury (Miller et al., 2006) (Nakagiri et al., 2007) (Simone et al., 2014) (Yokota et al., 2011). The induction of hypoxia inhibitory factor-1a (HIF-1a) by hypoxic conditions activates NOX. Additionally, phospholipase A_2, TNF-α, IL-1b and angiotensin II are all released during reperfusion and are also known to activate NOX (Dewald and Baggiolini, 1985). NOX produces O_2^- which is converted to H_2O_2 (Wu et al., 2018). The components of NOX (gp90phox) which are mainly involved in ROS production are present in phagocytic leukocytes and account for 50-100% of the increase in oxidant production under inflammatory settings, whereas production of oxidants by other forms of NOX present in non-phagocytic cells (vascular NOX) release less than 10% of the oxidants generated by leukocytes (Kalogeris et al., 2012, 2016). Additionally, oxidative stress leads to oxidation of tetrahydrobiopterin (BH_4), an essential co-factor necessary for NOS coupling. Oxidation of BH_4 leads to its reduction and uncoupling of eNOS which instead of $NO^·$ yields O_2^- (Landmesser et al., 2003) (Kalogeris et al., 2012; Wu et al., 2018).

Under normal physiologic conditions, mitochondria represent the largest intracellular source of ROS; the oxidant pool is increased even more under I/RI stress. Endogenous mitochondrial antioxidant capacity is also decreased during I/RI which also contributes to oxidative stress (Dhalla et al., 2000). Oxidative stress degrades and damages several classes of macromolecules including lipids, proteins & DNA which lead to changes in multiple cell signaling pathways (Kalogeris et al., 2012).

I/RI can also activate apoptosis, necrosis and autophagy pathways (Wu et al., 2018). ROS and Ca^{2+} overload during I/R leads to the opening of the mitochondrial permeability transition (MPT) pore which decreases ATP production and depletes ATP, leading to even greater ROS production, ionic imbalances, swelling and rupture of cells (*necrosis*) (Rothermel et al., 1997) (Kalogeris et al., 2012). Previously, the activation and translocation of the apoptotic-inducing proteins *Bax, Bak, Bid, Puma* and *BNIP3* into mitochondrial membranes have been studied in ischemic tissues (Metukuri et al., 2009) (Wei et al., 2006). I/RI in tissues has also been shown stimulate the release of *Omi/HtrA2*, caspase activators, and Endonuclease G, which cause nuclear DNA fragmentation during apoptosis (Kim et al., 2010) (Nielsen et al., 2008). While autophagy is upregulated during I/RI (Takagi et al., 2007), it often fails to fully clear dysfunctional mitochondria which evolve during reperfusion. This appears to reflect the ability of the high amounts of ROS and Ca^{2+} overload released in I/RI to overwhelm the autophagic clearance capacity which triggers opening of MPT, ultimately leading to cell death. Blocking of autophagy elevates tissue injury; conversely pharmalogic induction of autophagy has been shown to exert a protective influence in I/RI (Cardinal et al., 2009) (Han et al., 2018). Necrotic cells are potent immunostimulators that trigger Th1 cytokine production and immune cell infiltration. Furthermore, ATP released from apoptotic cells via pannexin1 channels acts as an attractant for phagocytes triggering additional successive waves of inflammation (Elliott et al., 2009) (Chekeni et al., 2010) (Eltzschig and Eckle, 2011).

Vascular leakage is another event which occurs during I/RI. Solute exchange is governed by the integrity of cell-cell junctions including tight and adherens junctions at apical and lateral surfaces and gap junctions and desmosomes at basal surface. The adherens junctions are mainly comprised of cadherins like E-, N-and VE-cadherins (in endothelium) and nectins, whereas tight junctions are mainly comprised of claudins, occludin and junctional adhesion molecules (JAMs e.g. JAM-A, JAM-C and PECAM-1) (Campbell et al., 2017; Dejana, 2004). I/R disrupts assembly and barrier properties of both tight and adherens junctions. There is an I/RI mediated increase in intracellular calcium levels which activates transcription factors e.g. NF-κB and lead to changes in tight and adherens junction protein expression, metalloproteinase mediated proteolysis and blood-brain barrier disruption (Davis et al., 2001; Sasaki et al., 2003).

Importantly, our lab has demonstrated that oxidants e.g. H_2O_2 can trigger the internalization of VE-cadherin (Kevil et al., 2000) as early as 5 mins following exposure to these mediators with similar transient changes in cell surface VE-cadherin observed with exposure to histamine, another inflammatory mediator and to EDTA. These events were seen to depend on actin-filament binding and activation of PKC. The internalization of junctional elements e.g. VE-cadherin from the cell surface withdraws these junctional elements from participating in cell-cell opposition and explains how changes in the spatial organization of junctional proteins create disturbances in solute permeability in inflammation like I/RI.

The release of ROS, chemokines e.g. RANTES and prostanoids e.g. PAF and LTB_4 cause phosphorylation and degradation of endothelial junctional molecules (Kumar et al., 2009) (Kalogeris et al., 2012). Previously, it has been shown that claudin-1, ZO-1 and ZO-2 translocate from the plasma membrane to the cytoplasm under hypoxic conditions (Bednarczyk and Lukasiuk, 2011). VEGFR-2 dependent phosphorylation of occludin and loss of ZO-1 has been demonstrated in retinal ischemia reperfusion (Muthusamy et al., 2014). The significant reductions in the expression of adherens junction protein, N-cadherin, and increase in active form of gap junction protein, connexin 43, has been found in heart I/RI rabbit models (Tansey et al., 2006). The endothelial actin cytoskeleton is involved in the maintenance of cell-cell adhesion complexes and cell-matrix adhesion complexes and have been shown to be disrupted during acute forms of kidney injury. The detachment of endothelial monolayers from the extracellular matrix has also been observed during renal ischemia leading to greatly increased permeability of glomerular monolayers and loss of the endothelial barrier function (Sutton, 2009). Therefore, cell detachment and internalization of cell-cell junctional molecules represent important processes which lead to increased vascular permeability and tissue edema in I/RI.

Dead cells and/or damaged contents such as ATP, heat shock protein, S100 proteins are collectively known as 'damage associated molecular patterns' (DAMPs). Binding of DAMPs to toll-like receptors (TLRs) expressed on immune cells elicit inflammatory responses and activate macrophages, dendritic cells, endothelial cells to mobilize the complement cascade. Increases in cytosolic calcium and ROS generation during I/RI can also activate macrophages, neutrophils and endothelial cells (de Groot and Rauen, 2007; Kalogeris et al., 2012). ROS stimulate leukocyte-endothelial adhesion (Alvarez and Sanz, 2001) and

decrease the bioavailability of NO which normally inhibits leukocyte-endothelium binding, diminution of NO can intensify inflammation several-fold (Pierini and Bryan, 2015). NF-κB also regulates the expression of Bcl-2, TNF-α, ICAM-1, VCAM-1 and E-and P-selectin indirectly activating inflammation and apoptosis. Normally, NF-κB is inactive, however, I/RI activates NF-κB and pharmacological inhibition of NF-κB has been shown to suppress many features of I/RI injury (Matsui et al., 2005; Wu et al., 2018). TNF-α, upon binding to its receptors also activates NF-κB and induces expression of adhesion molecules (Son et al., 2004). ROS also increase intracellular calcium levels leading to activation of non-specific activation of proteases (metalloproteinases or 'MMPs') and phospholipases which drive the synthesis of pro-inflammatory prostaglandin mediators such as leukotrienes, thromboxane as well as platelet activating factor (PAF), and lysophosphatidic acid (Peplow and Mikhailidis, 1990) (Kerrigan and Stotland, 1993). Leukotriene B_4 (LTB_4) is a potent chemoattractant for leukocytes which increases neutrophil adhesion, transmigration and release of ROS and proteolytic enzymes from neutrophil granules (Bomalaski et al., 1990) (Christmas et al., 2006). Similarly, PAF promotes platelet accumulation, aggregation, increases vascular permeability and also increases leukocyte activation (Stokes and Granger, 2012) (Kubes et al., 1991) (McDonald, 1994). Activated neutrophils release ROS, additionally macrophages, endothelial cells and platelets can also release significant levels of ROS, protease, elastase and cytokines such as TNF-α, IL-8 which all provide chemotactic signals for neutrophils maintaining the inflammatory milieu, sustaining cytotoxicity and cell injury (de Groot and Rauen, 2007; Eltzschig and Collard, 2004; Kalogeris et al., 2012).The disruption of the vascular endothelial barrier after hypoxic insults also potently triggers neutrophil trafficking which further disrupt tissue integrity and cause extravascular fluid leakage and edema formation (Eltzschig and Collard, 2004).

Heparin-binding protein (HBP) is one factor released by neutrophils that causes calcium-dependent cytoskeletal changes in endothelial cells which cause vascular leakage (Eltzschig and Collard, 2004). Leukocyte-endothelial aggregation, platelet-leukocyte aggregates and fluid accumulation in tissues leads to the 'no-reflow' phenomenon causing continuous organ dysfunction even after reperfusion (Reffelmann et al., 2003) (Maxwell and Lip, 1997).

The complement factors C3a, C5a, iC3b and C5b-9, are all known to be activated during I/RI. The complement cascade can also induce the expression of VCAM-1, ICAM-1, E-selectin and P-selectin which all drive leukocyte trafficking and recruitment in I/RI. C5a stimulated leukocyte activation also induces the release of pro-inflammatory cytokines such as IL-1b, IL-6, MCP-1 and TNF-α (Collard et al., 1999) (Czermak et al., 1999). C5b-9 can also induce expression of IL-8 and MCP-1 and can inhibit endothelial-dependent vasodilation (Stahl et al., 1995) (Kilgore et al., 1997) (Collard et al., 1999). JAK/STAT signaling pathway transduces signals for various cytokines and growth factors e.g. IL-2, IL-6, IFN-γ and PDGF and thus plays a role in cell proliferation, migration and apoptosis. The pharmacological inhibition of the JAK/STAT pathway has been shown to attenuate experimental renal I/RI in rats (Yang et al., 2008).

1. Stem cells

Stem cells (SC) are unspecialized cells with the ability to self-renew and differentiate to one or more developmental 'fates. SC are critical in tissue homeostasis and repair (Kolios and Moodley, 2013). Differentiation potential of stem cells varies among stem cells and depends mainly on their origin (Rossant, 2001b). According to their differentiation potency, all stem cells can be categorized into five different groups (Fig. 1): 1-Totipotent or omnipotent which can differentiate to all types of cells in the body (Rossant, 2001a); 2-Pluripotent which can produce all cell types, excluding cells of the embryonic membrane (Takahashi and Yamanaka, 2006); 3-Multipotent stem cells are able to differentiate into many, but not all cell types (Ratajczak et al., 2012); 4-oligopotent cells can divide and self-renew but without differentiation (Majo et al., 2008); 5-unipotent stem cells can self-renew and differentiate into a single lineage (Overturf et al., 1997).

Although stem cells are found in many different sources, they share many common properties, still differ in terms of rates of differentiation, secretion of trophic factors, as well as the ability to be stimulated by endogenous signaling mechanisms under pathologic conditions (Kalladka and Muir, 2014).

1.1. Stem cell classification based on their origin

Stem cells can be classified, based on their origin, into 5 different groups of embryonic, fetal, perinatal, adult, and iPS (Fig. 1) (Ilic and Polak, 2011) (Kolios and Moodley, 2013).

1.1.1. Embryonic stem cells (ESCs)

Embryonic stem cells (ESCs) which are derived from the inner cell mass of pre-implantation embryo, possess the capability of unlimited self-renewal and expansion (Hao et al., 2014; Madigan and Atoui, 2018; Nadig, 2009). ESCs are also pluripotent meaning that they have the ability to differentiate into all cell types of the organism under specific culturing condition *in vitro* (Broughton et al., 2012).

Major limitations regarding the use of ESCs include ethical issues, immune rejection, their fetal age, its malignant transformation to tumor following transplantation, and limited sources (Hao et al., 2014) (Broughton et al., 2012).

1.1.2. Fetal stem cells

Fetal stem cells are cell types isolated from fetal tissues and can differentiate into the various organ systems of the body. There is an abundant literature suggesting that fetal stem cells have greater plasticity and a higher capacity for replication compared to adult stem cells (O'Donoghue and Fisk, 2004). Fetal stem cells can be divided into neural crest stem cells, fetal hematopoietic stem cells, and fetal mesenchymal stem cells (Beattie et al., 1997).

1.1.2.1. Neural crest stem cells. Neural crest cells are a transient stem cell-like population that form in the dorsal neural plate border during neurulation (Liu and Cheung, 2016) (Nyffeler et al., 2017) and then they migrate to their target sites during development, where they can differentiate into variety of cell types such as sensory neurons, glia, melanocytes, adrenal medulla, and cranial cartilage/bones (Nyffeler et al., 2017) (Villa et al., 2000).

1.1.2.2. Fetal hematopoietic stem cells. Like other stem cells, HSC collected from fetal blood have the capacity of self-renewal and proliferation, but at a higher rate (shorter doubling time) compared to those found in cord blood or adult bone marrow-derived SC (O'Donoghue and Fisk, 2004). Both adult and fetal HSC are characterized by the expression of 'hematopoietic' CD34 antigen, as well as absence of CD38 and HLA-DR markers (Madigan and Atoui, 2018; O'Donoghue and Fisk, 2004).

1.1.2.3. Fetal mesenchymal stem cells (fMSCs). fMSCs are multipotent stromal cells which have higher self-renewal and differentiation capacity (O'Donoghue and Chan, 2006); (Ljung et al., 2019), longer telomerase, superior telomerase activity when compared to adult mesenchymal stem cells (Campagnoli et al., 2001); (Rufaihah et al., 2018).

1.1.3. Perinatal stem cells

Perinatal (infant) stem cells can be easily obtained at birth from extra-embryonic structures such as amniotic fluid (AF) (Prasongchean et al., 2012), umbilical cords (UC) (Majore et al., 2011), and placenta membranes (Balbi and Bollini, 2017) (Abbaspanah et al., 2018).

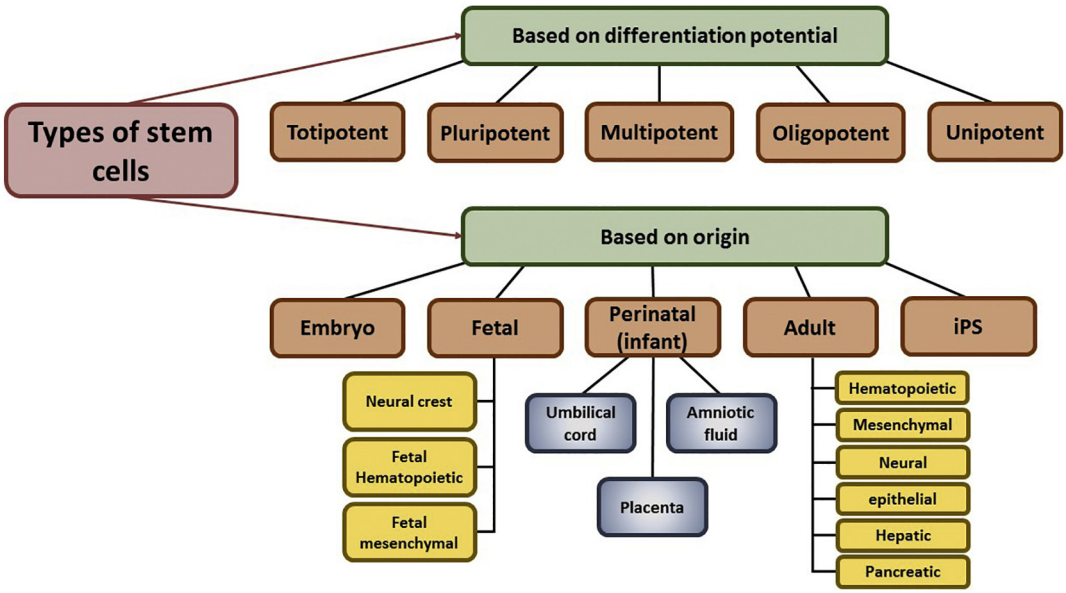

Fig. 1. Classification of stem cells.

1.1.3.1. Amniotic fluid stem cells. Amniotic fluid contains multiple cell types, mainly with mesenchymal properties including self-renewal and differentiation potential (In 't Anker et al., 2003). Amniotic fluid-derived mesenchymal stem cells can be collected during pregnancy via amniocentesis or at the end of gestation (Balbi and Bollini, 2017).

1.1.3.2. Umbilical cord stem cells (UCSC). Umbilical cord blood collected post-natally is the most abundant source of stem cells, particularly hematopoietic and mesenchymal stem cells (Weiss and Troyer, 2006). UCSC which are fibroblast-like, spindle-shaped cells have been easily extracted and expanded *in vitro* without losing their immunomodulatory properties (Madigan and Atoui, 2018).

1.1.3.3. Placenta-derived stem cells. The human placenta has been recognized as a rich source of stem cells based on the expression of pluripotency markers on hPMSC, and their demonstrated ability to differentiate into multiple different cell lineages, in addition to their ability to secrete paracrine factors with anti-inflammatory, anti-bacterial, anti-fibrotic actions (Azizian et al., 2018) (Beeravolu et al., 2017) (Bollini et al., 2018). Different stem cell-like populations can be isolated from different parts of placental tissues including human amniotic epithelial cells (hAEC), amniotic mesenchymal stromal cells (hAMSC), chorionic mesenchymal stromal cells (hCMSC), human umbilical cord mesenchymal stem cells (hUCMSC), and placenta-derived adherent cells (PDA-001). Placental-derived stem cells express cell surface markers which have previously identified in bone marrow-derived stem cells (e.g. CD13, CD29, CD44, CD73, CD90, CD105, CD166, MHC I) and pluripotent stem cells (e.g. SSEA4, Tra-160, Tra-181, Oct-4, Nanog, or Sox-2) (Xu et al., 2018) (Maximova et al., 2017) (Mathew and Bhonde, 2017) (Bollini et al., 2018).

The placenta could be a significant source of therapeutic SC since it is a very rich source of stem cells which can be readily obtained, without the need of invasive procedures for isolation and without ethical complications (Mathew and Bhonde, 2017) (Talwadekar et al., 2015). The unique immunomodulatory properties of placenta-derived stem cells in suppression of proliferation, maturation and function of T-cells, macrophages, and monocyte-derived dendritic cells make them a suitable source of MSCs (Del Fattore et al., 2015; Shehadah et al., 2014).

PDACs (placenta-derived adherent cells) are characterized by their $CD34^-$, $CD10^+$, $CD200^+$, and $CD105^+$ expression. The intramuscular injection of PDAC stimulates vascular remodeling, attenuates oxidative stress, and improves limb function. PDAC represent an important therapeutic tool that requires no histocompatibility tissue matching and is far more convenient and expeditious to use compared to BM or adipose-derived MSC. PDA-001 is a standardized formulation of PDAC which is being used intravenously for the treatment of Crohn's disease (Wu et al., 2017) (Shehadah et al., 2014).

1.1.4. Adult stem cells (ASCs)

ASCs, also known as tissue resident stem cells, are found in post-natal individuals, and are either multi- or unipotent (Kolios and Moodley, 2013). Multipotent ASC can be further categorized as hematopoietic stem cells (HSC) (Gilbert et al., 2012), neuronal stem cells (NSC), and mesenchymal stem cells (MSC) (Dulak et al., 2015) (Liu et al., 2016). Epidermal stem cells (ESC) are classified as unipotent adult stem cells which have the ability to differentiate into only one cell type; e.g. keratinocytes (Dulak et al., 2015).

1.1.4.1. Hematopoietic stem cells (HSCs). HSCs comprise a heterogenous population of cells that normally resides in the bone marrow (Morrison and Scadden, 2014). HSCs have the ability to self-renew and differentiate into the most hematopoietic system lineages such as myeloid, lymphoid, megakaryocytic, and erythroid (Upadhaya et al., 2018) (Christensen and Weissman, 2001). HSCs are critical for maintaining the blood system through hematopoiesis throughout the lifetime of an organism (Tajer et al., 2019).

1.1.4.2. Neural stem cells (NSCs). Endogenous NSCs: endogenous NSCs, located in the dentate gyrus of the hippocampus, the sub-ventricular zone (SVZ), and the olfactory bulb (Zhou et al., 2019) (Lakshman et al., 2018), act mainly by producing neurotrophic factors such as NGF and glial cell line-derived neurotrophic factor (GDNF); releasing proangiogenic complexes (netrin-4, laminin, and integrins); regulating the inflammatory environment; and secreting factors to promote synaptic plasticity such as thrombospondins (Stenudd et al., 2015) (Xu et al., 2019) (Hao et al., 2014).

Exogenous NSCs: Major potential sources of exogenous NSCs could include ESCs, iPSCs, bone marrow and adipose-derived MSCs, embryonic NSCs, and stem cells from the fetal and adult nervous system. These cells are able to proliferate in the presence of various growth factors such as EGF, FGF, and leukemia-inhibiting factor (LIF), and differentiate into neurons, astrocytes, and oligodendrocytes (Koch et al., 2009) (Hou et al., 2017) (Hu et al., 2019) (Hao et al., 2014) and

may support and restitute components of the central and peripheral nervous system.

1.1.4.3. Mesenchymal stem cells (MSCs). MSCs are defined as multipotent cells with the capacity for self-renewal (da Silva Meirelles et al., 2008). MSCs have been isolated from almost all mesodermal layers of mesenchymal tissues including circulating blood (Wang et al., 2008), adult and fetal bone marrow (BM), spleen, cartilage, muscle tendons (Salingcarnboriboon et al., 2003), adipose tissues (Zuk et al., 2001), periosteum (Nakahara et al., 1991), synovial fluid (De Bari et al., 2001), thymus, trabecular bone, dermis, dental pulp and the lung (Hao et al., 2014; Ishikawa et al., 2013; Kalladka and Muir, 2014; Merino-Gonzalez et al., 2016; Sabatini et al., 2005).

The major criteria to define MSCs, based on the *'Society for Cellular Therapy'* proposal, include plastic adherence of the isolated cells in culture, the expression of CD105, CD73, and CD90, and their lack of expression of CD34, CD45, CD14 or CD11b, CD79a or CD19, and HLA-DR in more than 95% of the culture, and ultimately, the differentiation of MSCs into osteoblasts, adipocytes, chondroblasts, neural cells, hepatocytes, insulin-producing cells, and numerous additional cell types (Thomson et al., 1998).

A remaining and major concern regarding the source of MSCs has been how to optimize an isolation procedure in order to obtain enough cells from a single donor (Del Fattore et al., 2015) which is still a technical challenge for therapy.

1.1.4.4. Epithelial stem cells. The continual cell replacement of epithelial tissues during homeostasis is directly supported by epithelial stem cells which have the capacity for self-renewal and differentiation (Li et al., 2018b) (Zhou et al., 2016). Epithelial stem cells mostly reside in intestine and epidermis both of which are typical epithelial tissues (Boehnke et al., 2012). Epithelial stem cells exhibit many diverse morphological and functional characteristics; moreover, they show substantially different homeostatic turnover rate (Fuchs, 2009) (Blanpain et al., 2007). For example, the intestinal epithelium is completely self-renewed within ~5 days, while interfollicular epidermis takes ~4 weeks to be replaced (Blanpain et al., 2007).

1.1.4.4.1. Gastrointestinal epithelial stem cells. Gastrointestinal stem cells are located in a "niche" in the intestinal crypts and gastric glands, and are responsible for the continuous renewal and regeneration of the mucosal epithelium both normally and after injury (Rao and Wang, 2010; Kalita et al., 2019; Rao and Wang, 2010).

1.1.4.4.2. Epidermal stem cells. Skin epidermal stem cells which reside in the basal layer of the inter-follicular epidermis, are capable of continual self-renewal and differentiation to repair the epidermis and maintain tissue homeostasis after injury (Veltri et al., 2018) (Jackson et al., 2017). Epidermal stem cells are considered to be multipotent adult stem cells that could be beneficial in treatment of different skin diseases including pemphigus and epidermolysis bullosa (De Rosa et al., 2014) and stable vitiligo (Falabella et al., 1992).

1.1.4.5. Hepatic stem cells. Longstanding liver injury activates functional stem cells of the liver which are located within the intrahepatic biliary tree (Bautista et al., 2019) (Alison et al., 2007). These so called hepatic stem cells can give rise to cords of bipotential hepatic progenitor cells, and ultimately differentiate into hepatocytes and biliary epithelial cells (Liu et al., 2019b). Bone marrow also contains a population of stem cells with hepatic potential which may contribute to hepatocyte regeneration when it becomes reprogrammed for liver recovery (Lagasse et al., 2000).

1.1.5. Induced pluripotent stem cells (iPS)

iPS cells are embryonic stem (ES) cell-like cells that are reprogrammed from differentiated somatic and germ cells by the induction of specific transcription factors (Yu et al., 2007); (Awe et al., 2013) (Li et al., 2018a) (Takahashi and Yamanaka, 2013). iPS cells have the capacity of unlimited self-renewal and differentiation to create all three germ lines. The advantage of using iPS cells include the generation of iPS cells from a patient's own somatic cells (such as fat cells, nerve cells, skin fibroblast, B cells, T cells, peripheral blood mononuclear cells) without ethical issues (Li et al., 2018a). While the risk of rejection of iPS cells has been shown to be low when administered to the same individual, it has been reported that the immunogenicity of iPS cells could change because of fatal errors or mutations during reprogramming and differentiation processes (Li et al., 2018a; Takahashi and Yamanaka, 2013; Yasuda et al., 2018).

2. Stem cell therapy

Stem cell characteristics make them valuable candidates in a wide range of biological and medical applications (Chien, 2008). Stem cells provides the opportunity to investigate and develop more effective and safer therapies with the capability to replace and regenerate damaged tissues (Lodi et al., 2011) (Inoue and Yamanaka, 2011).

While stem cells have been studied extensively for their ability to differentiate into variety of cell types, recent studies have also suggested that acute beneficial effects of stem cells depend instead on their *paracrine* signaling actions (Park et al., 2018) (Tachibana et al., 2017) (Merino-Gonzalez et al., 2016). Paracrine function of stem cells are related to the secretion of several trophic factors including cytokines, chemokines, and extracellular matrix protein into the surrounding environment (Mirotsou et al., 2011) (Hao et al., 2014; Merino-Gonzalez et al., 2016), which might act as trophic immunomodulators, angiogenic factors, anti-apoptotic factors, antioxidants molecules and cellular chemotaxis-inducers (Mancuso et al., 2019) (Tsuji et al., 2018) (Merino-Gonzalez et al., 2016) (Fig. 2). MSCs exert their beneficial effects by introducing neurotrophic factors such as HGF, VEGF, NGF, BDNF, bFGF, FGF-2, and IGF-1 into the environment which maintains survival of many cell types including neurons. It has been reported that extracellular vesicles and microvesicles (MVs) released from MSCs also contribute to these 'paracrine' forms of signaling (Liu et al., 2019a) (Li et al., 2019) (Merino-Gonzalez et al., 2016).

In the next section of this review, we discuss potential protective mechanisms of stem cells in the setting of ischemia-reperfusion injury of several organs including brain, heart, liver, intestine, kidney, and eye. Fig. 3 describes the protective effects of stem cells in organ-specific IR injury.

2.1. Stem cells in ischemic stroke

Stroke remains the main cause of severe disability and mortality in adults (Rodrigo et al., 2013) (Tong et al., 2019) (Hao et al., 2014). The incidence and occurrence of stroke has increased with changing demographics of aging in both developed and developing countries. Thromboembolism accounts for up to 85% of the forms of cerebral ischemia, while hemorrhage resulting from hypertension or vessel wall pathology accounts for the remainder (15%) of strokes (Amarenco et al., 2009) (Adams Jr. et al., 1993) (Mozaffarian et al., 2016) (Kalladka and Muir, 2014). Ischemic stroke is defined as a sudden occlusion of one or more cerebral arteries due to either thrombosis or embolus, and provokes an acute loss of neurons, astroglia, oligodendroglia and causes disruption of cortical synaptic structure (Sacco et al., 2013) (Hao et al., 2014; Kim et al., 2018).

Several complex molecular events frequently lead to irreversible tissue injury following cerebrovascular occlusion, including failure of energy synthesis, loss of transmembrane ionic gradients, neuronal cell depolarization and excitotoxicity (Murphy et al., 2008) (Kalladka and Muir, 2014). Other processes involved in ischemic injury include localized inflammatory responses with infiltration of neutrophils and macrophages from the blood into brain tissue and impairment of the blood brain barrier (Siesjo, 1992) (Chamorro and Hallenbeck, 2006) (Kalladka and Muir, 2014). Early functional recovery of damaged tissue

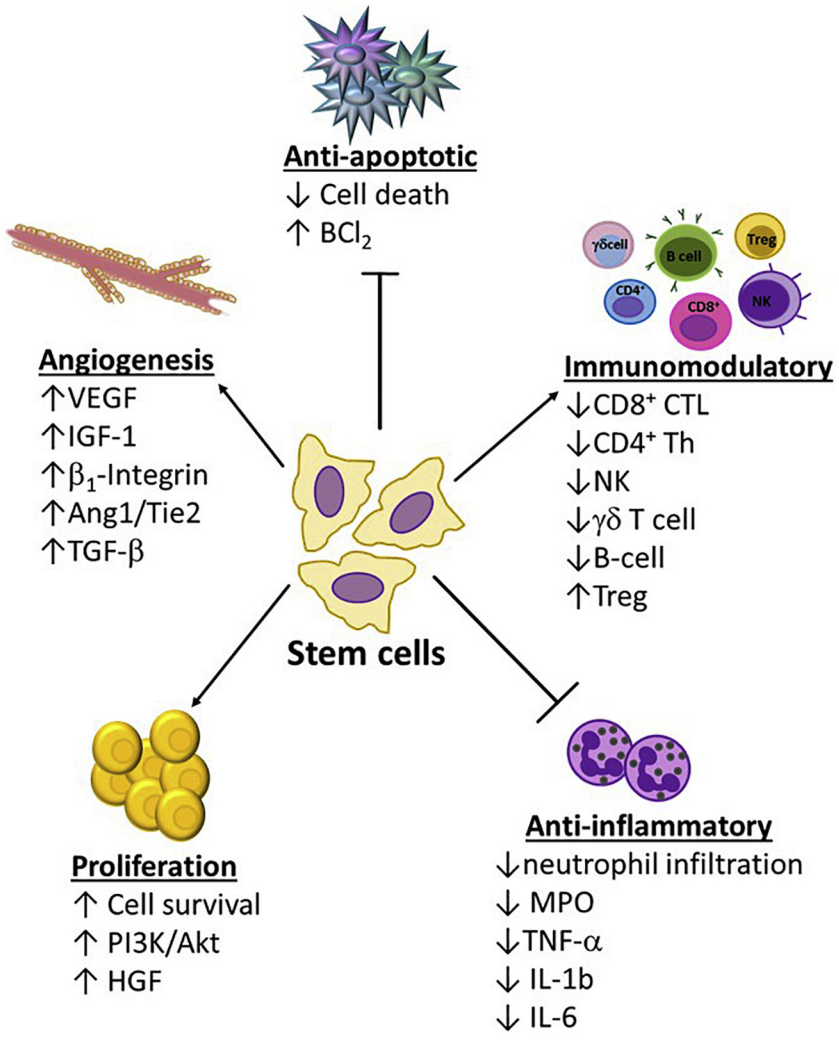

Fig. 2. Paracrine functions of stem cells.

around the infarcted area could reflect the resolution of edema and inflammation, however, immunomodulation, angiogenesis, endogenous neurogenesis, and altered gene expression might also be involved in long term recovery of ischemic brain tissue (Amantea et al., 2009) (Stanimirovic et al., 1997) (Kalladka and Muir, 2014). Mechanistically, stem cell therapies have been demonstrated to be effective in endogenous recovery of injured tissue from ischemic stroke, which depends critically upon the timing and method of their administration (Del Fattore et al., 2015).

Several studies revealed that many types of adult stem cells circulate in peripheral blood and then become directed to migrate towards sites of injury, where they contribute to tissue repair (Merino-Gonzalez et al., 2016). Upon injury, bone marrow-derived stem cells (including hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs), and very small embryonic like stem cells (VSELs)) can all be mobilized from the bone marrow and migrate into the systemic vasculature (Jeong et al., 2003). These cell types can then penetrate the central nervous system and help to improve neuronal injury (Ishikawa et al., 2013). This process can be brought about by activation of cerebral vascular endothelial cell which supports rolling and adhesive molecules (Ruster et al., 2006) as well as by oxidant (H_2O_2) mediated-activation of integrins on stem cell (Kavanagh et al., 2015) which increases their binding to endothelial adhesive determinants.

Therefore, in response to brain injury, the CNS recruits mobilized HSC and promotes their migration into tissues both by releasing neurotransmitters from nerve terminals within bone marrow and through sympathetic release of neurotransmitters into blood circulation (Ishikawa et al., 2013). Homing of MSCs begins within the active inflammatory zone in the injured tissue from which homing signal originated (De Becker and Riet, 2016) (Ishikawa et al., 2013) (Kalladka and Muir, 2014). The preferential migration of intravenously or intracerebrally injected MSCs to the ischemic sites might be mediated by factors including SDF-1 (Ruster et al., 2006), IL-8 (Coultas et al., 2005), MCP-1 (Belema-Bedada et al., 2008), MIP-1a (macrophage inflammatory protein-1a) (Wu et al., 1990) (Thored et al., 2006), VEGF (Walter et al., 2005) or CXCL12 (Levesque et al., 2003) chemokine receptors (Hao et al., 2014; Ishikawa et al., 2013; Kalladka and Muir, 2014). In the ischemic brain, increased migration of neuroblasts to peri-infarct regions is mediated by soluble molecules and their receptors, including angiopoietin-1 (Ang1)/Tie2, stromal derived factor-1a/chemokine receptor 4 (CXCR4) (Zhang et al., 2016).

Increased levels of neurotrophic factors such as SDF-1, VEGF-A, GDNF, BDNF, NGF, IGF, EGF, and bFGF might help provide a basis for suppression of apoptosis, glutamate excitotoxicity, and oxidative stress and the increased neuron survival and anti-inflammatory activities seen with MSCs in the treatment and recovery from ischemic brain injury (Hao et al., 2014). Systemically (intravenous) administered NSCs efficiently emigrate to injured ischemic area and release neuroprotective cytokines like VEGF-A (Harms et al., 2010), BDNF (Kurozumi et al., 2004) (Benraiss et al., 2001), GDNF, FGF-2 (Ikeda et al., 2005), NGF, and neurotrophins which promote angiogenesis, immunomodulation,

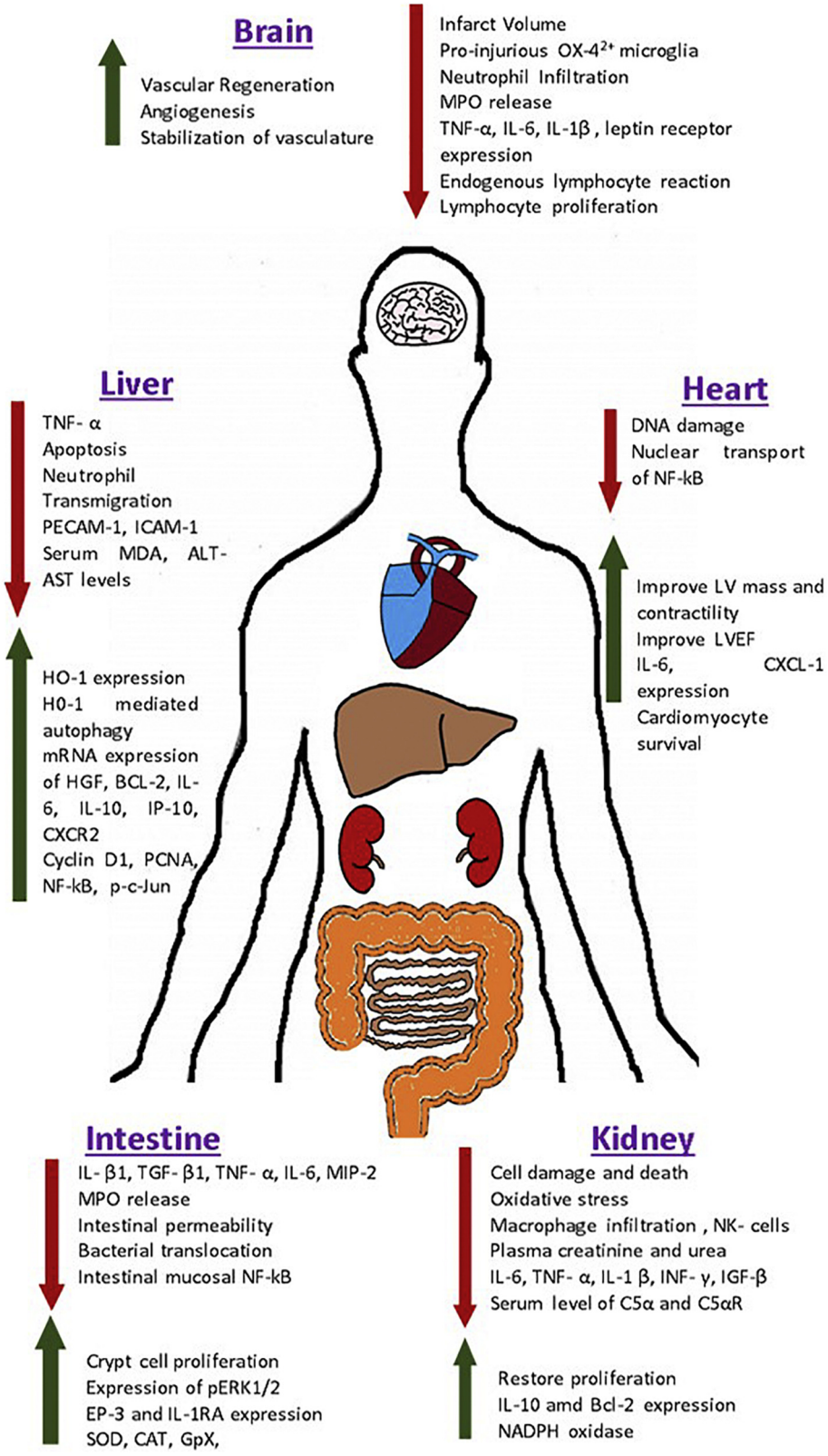

Fig. 3. Organ specific effects of stem cells in IR injury.

and endogenous neurogenesis after ischemic stroke (Chen et al., 2013; Hao et al., 2014; Kalladka and Muir, 2014). Conversely, overexpression of neuroprotective factors such as Bcl-2, adenosine, and myocyte enhancer factor 2C in ES-cell derived cells have also been shown to be protective in stroke models (Ishikawa et al., 2013).

Proteomic analysis has demonstrated that MSC-derived vesicles contain and release growth factors such as VEGF-A, TGFβ1, and IL-8, all of which contribute to pro-angiogenic activities (Hao et al., 2014; Merino-Gonzalez et al., 2016). Furthermore, MSC-derived extracellular vesicles stimulate proliferation and migration of endothelial and

vascular smooth muscle cells via induction of transcription factors via HGF activation of LIF and STAT-1 that are involved in pro-angiogenic pathways (Merino-Gonzalez et al., 2016). It has been reported that conditioned medium collected from MSCs is able to significantly increase numbers of migrated endothelial cells (HUVEC) and increase capillary tube lengths in matrigel matrix (Yang et al., 2018) (Merino-Gonzalez et al., 2016). MSCs have been proven to be effective in suppression of inflammation post-ischemic stroke through induction of polyamine (e.g. putrescine) that promote actin filament reorganization (Alexander et al., 1987) and could alter the integrity of BBB in brain injury (Shin et al., 2016). Current studies have considered the ability of placental-derived mesenchymal stem cells to modulate the microenvironment in a way that promotes endogenous neurogenesis through increased vascular density, increased expression of vascular endothelial growth factors, and basic fibroblast growth factor (Ishikawa et al., 2013).

Animal studies of stem cells in ischemic stroke

Administration of MSCs can reduce infarct volumes and improve functional outcomes in models of stroke (Broughton et al., 2012). There are data showing that embryonic stem cell-derived neural progenitor cells transplanted into stroke mice contribute to the repair of damaged tissue. Similarly endothelial cell derived from ES cells potentially promote vascular regeneration and reduction of infarct volume in stroke mice models (Ishikawa et al., 2013). Moreover, intravenous delivery of NSCs reduces numbers of pro-injurious OX-42^{+} microglia, attenuates neutrophil infiltration and myeloperoxidase signal in brain lesions, and downregulates the expression of several inflammatory mediators including TNF-α, IL-1b, IL-6, as well as leptin receptors (Hao et al., 2014). Implantation of umbilical cord mesenchymal stem cells (UCMSCs) into ischemia-damaged areas of the brain in rats post-stroke induced beneficial angiogenesis and stabilization of the vasculature mediated by the angiopoietin (Ang)/Tie system (Zhao et al., 2015).

Intravenous administration of hPD-MSCs suppress both endogenous lymphocyte reaction due to expression of HLA-G, and mitogen-induced and allogeneic lymphocyte proliferation in CD4^{+} and CD8^{+} T cell populations (Chen et al., 2013). Double infusion of placenta derived MSCs (10ˆ6 cells) at 8 and 24 hours post-stroke improved functional outcomes; this was not achieved by a single injection of cells at 24h (Kranz et al., 2010; Shehadah et al., 2014). Administration of PDA001 positively influenced endothelial proliferation, vascular densities and perimeter into the ischemic brains of both young and older rats. Improvements in functional outcome recoveries with PDA001 administration 24 h after MCAo likely reflect neurorestorative rather than a neuroprotective effect (Shehadah et al., 2014). In both young and older rats, treatment with 10,000 PDA001 cells, significantly increased numbers of BrdU immunoreactive endothelial cells which indicates active angiogenesis. Injection of 4 million PDA001 cells 4h after MCAo significantly decreased TUNEL and cleaved caspase 3 abundance in the post-ischemic brain, however, it increased the expression levels of VEGF-A and HGF in the IBZ. In contrast to the idea that implanted stem cells are expected to migrate and replace the injured tissue, only a few of these PDA001 cells successfully migrated into the ischemic tissue (Chen et al., 2013). Increased levels of neuroblast production following ischemic stroke has been reported in the subventricular zone in both rats and human brain biopsy after stroke (Kalladka and Muir, 2014).

Cerebral endothelial cells have been shown to suppress proliferation of neural stem cells via interactions involving endothelial ephrinB_2 and Jagged1 with neural stem cell Notch and Eph. Integrins alpha-6 and beta-1 released from cerebral vasculature are also critical in regulation of biologic function of neural stem and progenitor cells (Zhang et al., 2016).

2.2. Stem cells in myocardial infarction

Acute myocardial infarction (AMI) represents the most common and devastating cardiovascular event worldwide, leading to ischemic heart damage by inducing apoptosis, necrosis, inflammatory responses, and remodeling (Madigan and Atoui, 2018). Ischemic heart damage triggers scar formation, ventricular stiffness, and unfavorably altered myocardial contractility (Cambria et al., 2017; Madigan and Atoui, 2018).

Most recently, stem cell therapy has shown to be a promising therapeutic approach for improving AMI outcomes (Carvalho et al., 2015) (Garbern and Lee, 2013) (Cambria et al., 2017; Madigan and Atoui, 2018). A meta-analysis on stem cell therapy suggests that SCT leads to significant decreases in mortality and rehospitalization, improved left ventricular ejection fraction (LVEF), and improved exercise capacity, and quality of life (Cambria et al., 2017). Several cell types including skeletal myoblasts (SMs), bone marrow mononuclear cells (BMMNCs), hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), and mesenchymal stem cells have been used for heart repair and regeneration (Katarzyna, 2017) (Schaun et al., 2016) (Cambria et al., 2017).

Mechanistically, MSC administration improved left ventricle ejection function post-MI through several mechanisms including differentiation into vascular endothelial and cardiomyocytes, recruitment of endogenous stem cells and paracrine signaling, although the differentiation of MSCs into cardiomyocytes remains highly disputed and controversial (Cambria et al., 2017; Madigan and Atoui, 2018).

Paracrine actions of MSCs activate homing of endogenous stem cells, and promote secretion of immunomodulatory and trophic factors that promote vascularization (Burchfield and Dimmeler, 2008) (Wang et al., 2012) (Cambria et al., 2017) (Madigan and Atoui, 2018). Administration of MSCs showed beneficial effects on mechanical, regenerative, and clinical outcomes in cardiac infarct model (Jeong et al., 2018). Comparing the effects of MSCs and bone marrow derived stem cells (BM-MSCs) in chronic ischemic heart disease showed that MSCs were more effective in improving heart function. Potential mechanisms which might have contributed to biological efficacy of MSCs therapy include: 1) differentiation of MSCs into cardiomyocytes or other structural cell types, 2) development of new blood vessels networks after MI, 3) secretion of paracrine mediators from MSCs, 4) stimulation of endogenous cardiac precursors to repair the injured tissues (Jeong et al., 2018). HSCs enhanced angiogenesis and vasculogenesis, potentially due to their paracrine effects but not through myocardial differentiation (Cambria et al., 2017).

Most recently, exosomes secreted from cardiomyocytes have shown to be effective in cell survival, angiogenesis, immune responses, and intercellular contacts (Hu et al., 2018). The secretome of stem cells cumulatively includes soluble paracrine factors as well as microRNA-enriched extracellular vesicles released by stem cells, which have demonstrated to be beneficial in regeneration of the injured myocardial tissues (Bollini et al., 2018).

However, several studies still reported higher vascular densities, increased cardiomyocyte survival and improvement of cardiac function following administration of amniotic fluid stem cells where it has been suggests that paracrine effects of stem cell-secreted factors promote cell-cell interactions and maintain a regenerative microenvironment for injured cardiac tissues (Danieli et al., 2015) (Bollini et al., 2018).

Therapeutic effects of placental stem cell on the injured cardiac tissues could be related to their cardiomyocyte differentiation potential or to the specific paracrine effects such as anti-apoptotic, pro-angiogenic, and immunomodulatory properties (Liu et al., 2015b) (Li et al., 2017b) (Bollini et al., 2018). Few studies provided evidence of differentiation of placenta stem cells toward cardiovascular and cardiomyocyte cells (Okamoto et al., 2007) (Bollini et al., 2018).

Animal studies of stem cells in MI

Bone marrow derived MSCs have become an attractive candidate for cell therapy in myocardial infarction (MI) due to their multi-lineage potential, high rate of proliferation, immune privileged status, and more interestingly, their ability to implant and apparently differentiate into cardiomyocytes and vascular cells in animal models of (Hu et al., 2018; Jeong et al., 2018). Intravascular injection of adipose tissue

mesenchymal stem cells (ATMSCs) for ischemic cardiomyopathy showed improvements in LV mass and contractility via differentiation of these cells into cardiomyocytes (Madigan and Atoui, 2018).

Hu et al., 2018 have reported that exosomes produced by cardiomyocytes significantly increase the expression of apoptosis-related proteins and apoptotic rate of BMSCs under oxidative stress conditions, suggesting an accelerated transplanted BMSCs injury in infarcted heart due to poor survival of transplanted cells (Hu et al., 2018).

Immature human amniotic-derived progenitors like amniotic fluid-derived mesenchymal stem cells (AF-MSC) and human amniotic FACS sorting stem cells (hAFSC), were seen to be more prone to acquire cardiomyocyte-like phenotype upon *in vitro* stimulation with rodent neonatal cardiomyocytes or chemical treatment with 5-aza-2'-deoxycytidine, TGF-β1, or by a mixture of hyaluronic, butyric and retinoic acid (Bollini et al., 2018).

Despite the extensive ex-vivo reprogramming of amniotic stem cells, there is a low rate of *in vivo* engraftment and differentiation of transplanted amniotic fluid stem cells in MI models. Lazzarini et al., 2016 demonstrated that paracrine cardio-protective potential of hAFSC conditioned media was through activation of the PI3K/Akt signaling pathway, decreased DNA damage, nuclear transportation of NF-kB, and upregulation of the NF-κB-regulated genes such as IL-6 and CXCL1 which maintain cardiomyocyte survival (Lazzarini et al., 2016).

Placenta-derived stem cells have been shown to be cardioprotective by inhibition of cardiomyocyte apoptosis both *in vivo* and *in vitro* (Zhao et al., 2016). Pro-angiogenic and proliferative potentials of different types of placenta-derived stem cells in infarcted myocardium are mainly mediated by exosomes and vesicles produced by the cells (Liu et al., 2015a; Zhao et al., 2016).

2.3. Stem cells in renal I/RI

In addition to stroke and ischemic heart disease, several studies have shown beneficial effects of stem cells in renal I/RI which is mainly characterized by tubular apoptosis and necrosis, glomerular injury and inflammation (Semedo et al., 2007). In addition to acute renal failure, renal I/R injury can lead to loss and/or delayed recovery of transplanted kidney functions (Si et al., 2015). Renal I/RI also lead to destruction of renal corpuscles, loss of almost all glomerular tufts, peritubular congestion, and cytoplasmic vacuolation, pycnotic nuclei and acidophilic hyaline casts in tubules. These effects were also reversed by an injection of stem cells at 72 hours (Yuan et al., 2017a).

As in other settings, combinations of stem cell homing, differentiation and secretion of paracrine effects of stem cells are thought to be important in suppression of renal I/R. It has been proposed that the extracellular vesicle (EVs) released from human-induced pluripotent stem cell–derived mesenchymal stromal cells (hiPSC-MSCs) can dampen *necroptosis*, a programmed form of necrosis, in renal I/RI by delivering specificity protein 1 (SP1), a transcriptional activator of SK1 into renal cells, thereby activating SK1 expression and SP1 formation, a potent ligand for cell growth and survival (Yuan et al., 2017a). Combined treatment with MSCs and stem cell derived-EVs had an additive beneficial effect on kidney restitution (Aghajani Nargesi et al., 2017; Chen et al., 2017; Gu et al., 2016; Zou et al., 2016). Several other *in vitro* and *in vivo* studies on mesenchymal stem cell derived EVs showed that these EVs can decrease cell damage and death, restore proliferation, reduce oxidative stress and expression of nuclear factor E2-related factor-2 involved in regulation of cellular oxidative stress, increase the expression of NADPH oxidase-2, decrease the number of injurious macrophages, decrease the number of natural killer cells, decrease the expression of pro-inflammatory cytokines, including TNF-α, IL-1β and chemokine C-X-C motif ligand-1 (CXCL1) after renal I/RI. These beneficial effects of EVs have been linked to either direct transfer of mRNAs and factors such as VEGF-A involved in these processes or down-regulation of microRNAs involved in apoptosis, hypoxia, mitochondrial fission and cytoskeletal reorganization (Aghajani Nargesi et al., 2017; Chen et al., 2017; Gu et al., 2016; Zou et al., 2016). MSCs secrete microRNA-233 directly to release onto renal tubular epithelial cells increase total cell viability and levels of several growth factors including hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), transforming growth factor beta (TGF-β), and vascular endothelial growth factor (VEGF) mainly by inhibiting NLR family-pyrin domain containing 3 (NLRP3) signaling which has been shown to play role in cytokine production and renal injuries (Yuan et al., 2017b). Lin et al., 2003 demonstrated that hematopoietic stem cells can differentiate into renal tubular cells and reduce renal I/RI (Lin et al., 2003). Stem cell factor (SCF) and granulocyte colony-stimulating factor (G-CSF) have been shown to mobilize the bone marrow stem cells (BMSCs) to site of tubular injury and thus repair injury from acute tubular necrosis (Bi et al., 2015).

Animal studies of SC in renal I/R

Rat models have shown that CD73, CD105 and CD90 positive MSC led to better renal outcomes after renal I/RI as shown by reduced plasma levels of creatinine and urea, increased kidney tissue levels of IL-4 (an anti-inflammatory cytokine) and reduced level of IL-1 β (a pro-inflammatory cytokine). Additionally, MSC-treated kidney tissues had more nuclei reactive for Proliferating Cell Nuclear antigen (PCNA), an essential factor for DNA polymerase activity and replication, support more early tubular regeneration compared to non-treated controls (Sadek et al., 2013; Semedo et al., 2007). Tang et al., 2018 showed that human bone marrow MSC (hBM-MSCs) led to the reduction in macrophage infiltration, serum levels of C5a and expression of C5aR and TNF-α & IL-1β, pro-inflammatory cytokines, in renal tissues in mice (Tang et al., 2018). The treatment of LPS-activated macrophages with hBM-MSCs *in vitro* led to decline in expression of C5aR, secretion of pro-inflammatory factors TNF-α, IL-6, and nitric oxide and activation of NF-κB signaling (Sadek et al., 2013). Sadek et al., 2013 also showed that induction of renal I/RI in rats led to partial or complete loss of the brush borders and basement membrane in tubules. These effects were reversed by injection of MSC after 72 hours, but not injection of cells at 24 hours (Sadek et al., 2013). Adipose tissue–derived mesenchymal stem cells (ADMSCs) also suppressed renal fibrosis and promotes tubular regeneration primarily by releasing *exosomes* which upregulate the expression of Sox 9, a transcription factor involved in kidney development (Zhu et al., 2017). Additionally, ADMSCs decreased renal apoptosis, injury score, proteinuria, serum creatinine and expression of proteins associated with inflammation in particular HGF and SDF1, IL-6, TNF-α, IL-1β, IFN-γ, TNF-α, IFN-γ, TGF-β and increased the expression of, IL-10 (an anti-inflammatory cytokine) and Bcl-2 (an anti-apoptotic factor) (Sheashaa et al., 2016; Zhang et al., 2017). Ischemic preconditioning has been shown to increase the potential of ADMSCs as evident by further increase in expression of HIF-1α, SDF-1α, CD31, and Ki67 and further decrease in expression of caspase-3 and CD45 compared to individual treatments (stem cells and ischemic preconditioning alone) (Hussein et al., 2016). Tian et al., 2017 demonstrated (in rats) that treatment with human urine-derived stem cells decreased serum creatinine, blood urea nitrogen levels, tubular injury scores, numbers of apoptotic cells and expression of INF-γ & IL-1β while increasing numbers of proliferating cells and mRNA expression levels of anti-inflammatory cytokines, in particular IL-10 and TGF-β1 (Tian et al., 2017).

Fahmy et al., 2017 concluded that human cord mesenchymal stem cell can reduce serum levels of creatinine, urea, uric acid and oxidative stress by increasing the levels of glutathione (GSH), catalase (CAT) and glutathione-S-transferase (GST) (Fahmy et al., 2017). Human and mouse-induced pluripotent stem cells attenuated the necrosis and apoptosis in renal tissues and suppressed blood urea and serum creatinine level after renal I/R while enhancing renal tubule recovery, cell proliferation, and the expression of anti-inflammatory factors in particular IL-10, FGF, and TGF-β and pro-renal tubular repair factors such as EGF, HGF, and PDGF (Li et al., 2015; Toyohara et al., 2015).

Conditioned culture medium derived from iPSC also attenuated

renal I/RI in rats by reducing ROS generation, suppressing p38-MAPK activation and decreasing the expression of TNF-α and NF-κB signaling (Tarng et al., 2016). Stem cell antigen-1, a common stem cell marker, has been shown to constitutively bind to TGFβ receptors I and II and lead to silencing of TGFβ receptor-mediated Smad signaling which is involved in formation of pro-inflammatory factors to improve renal function after ischemia acute kidney injury (Camarata et al., 2015). Qiu et al., 2014 demonstrated that umbilical cord mesenchymal stem cells decreased the expression of ICAM-1 and suppressed neutrophil infiltration into renal tissues after renal I/RI in rats (Qiu et al., 2014).

After homing to injured kidneys, human mesenchymal stem cells attenuated I/RI at least in part by changing macrophage polarization toward the anti-inflammatory phenotype "M2" and by increasing matrix metalloproteinase-9 activity (which acted to reduce levels of collagen α1(I) and IV) (Wise et al., 2014).

Bone marrow stem cells (when injected either prior to ischemia or with reperfusion) reversed the negative effects of I/R on renal mitochondrial respiration by preserving normal levels of electron fluxes, the electrochemical gradient for protons, ATP synthesis and mitochondrial ROS generation (Beiral et al., 2014). The intravenous injection of mesenchymal stem cells decreased tissue levels of malondialdehyde (MDA), whereas superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were increased upon the induction of renal I/RI (Zhuo et al., 2011).

2.4. Stem cells in intestinal I/RI

Intestinal I/R injury is associated with high morbidity and mortality, and frequently occurs during small bowel transplantation, abdominal aortic aneurysm surgery, cardiopulmonary bypass, strangulated hernias and hemorrhagic shock (Jiang et al., 2013). Intestinal I/R has devastating effects on mucosal permeability, villus structure, mitochondrial activity and can lead to translocation of pathogenic microbes into the circulation where they trigger systemic inflammation (Grootjans et al., 2010; Guan et al., 2009). Animal studies have successfully demonstrated the beneficial effects of the stem cells in attenuation intestinal I/RI.

Mechanistically, less is known about the mechanism underlying the beneficial effects of stem cells in intestinal I/RI. A study done on C57Bl/6 mice showed that homing of MSCs to injured gut is very limited; despite poor migration, MSCs were still able to exert anti-inflammatory effects and improve tissue perfusion of the jejunum and ileum (Kavanagh et al., 2015).

Animal Studies of SC in intestinal I/R

Mesenchymal stem cells (MSCs) increase superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (Gpx) activities, but decrease malondialdehyde (MDA) in the intestine following ischemic injury. MSCs also increased anti-inflammatory cytokines EP3 and IL-1ra while decreasing pro-inflammatory cytokines e.g. IL1β, TGFβ-1, TNF-α, IL-6, MIP2, and MPO (Inan et al., 2017). Additionally, MSCs have been shown to have a synergetic effect on intestinal I/RI in combination with electro-acupuncture and heparin-binding EGF-like growth factor, measured as improved intestinal histology and solute permeability, increased crypt cell proliferation and mucosal concentration of mRNA for SDF-1, CXCR4, EGF, EGFR as well as lower mucosal NF-κBp65 and serum pro-inflammatory cytokines (TNF-α, IL-6) levels (Geng et al., 2016; Watkins et al., 2013).

Liu et al., 2014 showed that the hepatocyte growth factor c-Met signaling pathway (HGF/c-Met) fulfills an important role in MSC migration towards the liver injured by intestinal ischemia-reperfusion, and that subsequent repair of the liver can be induced by MSCs (Liu et al., 2014). MSCs transplantation has been successful in decreasing the TNF-α content of the bowel mucosa and intestinal mucosal NF-κB expression. Furthermore, MSCs treatment increased expression of pERK1/2 in the intestinal mucosa and PCNA in bowel mucosa (Jiang et al., 2013). Bone marrow mesenchymal stem cells attenuated intestinal injury due to I/R by reducing intestinal permeability and villi injuries, ZO-1 downregulation, and tight junction disruption, thereby maintaining intestinal mucosal barrier, probably by regulating the levels of TNF-α (Jiang et al., 2011; Shen et al., 2013). The injection of MSCs at the beginning of reperfusion in the superior mesenteric artery occlusion model decrease injury to the intestinal barrier, suppressed bacterial translocation, and was able to lower levels of serum lactate (Abarbanell, 2010).

2.5. Stem cells in Hepatic I/RI

Liver I/RI is a major cause of diminished liver functioning following liver surgery and commonly occurs during liver resection or transplantation. Several factors contribute to hepatic I/R injury including disturbed mitochondria respiration and oxidative stress (Tartaro et al., 2018), intracellular calcium overload (Vasques et al., 2016), Kupffer cell activation (Cheng et al., 2019) neutrophil infiltration (Hamada et al., 2008) as well as cytokine and chemokine release (Cheng et al., 2019) (Hamada et al., 2008) (Guan et al., 2014; Vasques et al., 2016).

While stem cells administered therapeutically often accumulate in the spleen and liver, they can be further 'encouraged' to reach this compartment. For example, intraportally injected BM-MSCs were found to migrate into spleen and liver, rather than the brain, kidney, or lung tissues in a rat liver I/R model (Nowacki et al., 2015).

Another study showed the equal distribution of MSCs to ischemic and non-ischemic parts of the liver after systemic injection of labelled MSCs (Isbambetov et al., 2016). However, when Saat et al., 2016 intravenously infused MSCs 2 hours before, or 1 hour after partial hepatic ischemia/partial hepatectomy, many cells were trapped in the lungs instead of migrating to the damaged liver (Saat et al., 2016).

The exosomes derived from human-induced pluripotent stem cell-derived mesenchymal stromal cells (hiPSC-MSCs) protected against liver ischemia-reperfusion, revealed as a decrease in hepatocyte necrosis, sinusoidal congestion and serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (Du et al., 2017; Haga et al., 2017; Nong et al., 2016). This exosome treatment also increased expression of proliferating cell nuclear antigen (PCNA) and phosphohistone-H3. The authors concluded that exosome protection involves direct fusion of exosomes with injured hepatocytes with increased rate of sphingosine kinase and formation of sphinhosine-1–phosphate (Du et al., 2017). Exosomes also decreased expression of TNF-α, IL-6 and HMGB1 and the apoptotic markers (caspase-3; Bax) with increased expression of antioxidants; GSH, GSH-Px and SOD (Haga et al., 2017; Nong et al., 2016).

Animal Studies of stem cells in hepatic I/R

Wang et al., 2018 showed that bone marrow mesenchymal stem cells suppressed liver ischemia–reperfusion injury by promoting expression of heme-oxygenase-1 (HO-1) and thus promoting HO-1 mediated autophagy (Wang et al., 2018). Mesenchymal stem cell therapy improved the survival rate and decreased ischemia reperfusion injury by up-regulating mRNA expression of HGF, Bcl-2, Bcl-XL, IL-6, IL-10, IP-10, and CXCR2 and downregulating TNF-α. MSC therapy also increased the expression of p-c-Jun, cyclin D1, PCNA and NF-κB (Wang et al., 2014). Saidi et al., 2014 showed that human adipose derived mesenchymal stem cells improved survival, numbers of regenerating cells and decreased serum IL-6 and alanine aminotransferase release (Kanazawa et al., 2011; Saidi et al., 2014). MSCs also attenuated liver I/R by reducing apoptosis and liver enzyme levels and increasing N-acetyltransferase-8 (NAT8) (Fu et al., 2014). Pan et al., 2012 concluded that MSCs confer protection by inactivating the MEK/ERK pathway (Pan et al., 2012). Human adipose derived stem cells and elements of their secretome decreased serum levels of IL-6, lowered neutrophil transmigration and decreased ICAM-1 and PECAM-1 expression, all of which improved histologic scores in a mouse hepatic I/R model (Lee et al., 2015).

Rats transplanted with BM-MSCs via the portal vein show partial

attenuation of liver I/RI with lower serum ALT and AST levels, lower malondialdehyde (MDA) levels and maintaining superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities. These stem cell treated rats also had fewer apoptotic hepatocytes and lower levels of BAX and caspase-3 (Jin et al., 2013).

2.6. Stem cells in retinal I/RI

Diabetic retinopathy, glaucoma and age-related macular degeneration remain the most common causes of irreversible blindness in western countries where retinal ischemia, cell death and inflammation are central events in vision loss. Current treatments such as intraocular injection of anti-VEGF and surgery can arrest the progression of disease but do not affect the damaged retina (Mathew et al., 2019). Therefore, there is a pressing need of a new and safer treatment. In this setting, stem cells have proven benefits in retinal I/R injury which are mediated both by stem cell-derived extracellular vesicles (EVs) and stem cell differentiation.

An *in vitro* model using an oxygen-glucose deprivation (OGD) of retinal ischemia showed that cell death was reduced, and cell proliferation improved following treatment with MSC-derived EVs. The endocytosis of EVs occurred in caveolar dependent fashion and mediated by heparin sulfate proteoglycans (Mathew et al., 2019). The authors also showed the beneficial effects of MSC-EVs *in vivo*. when EVs were injected into the vitreous humor 24hr following retinal ischemia inflammation and apoptosis decreased and functional recovery was improved (Mathew et al., 2019). Bone marrow stem cell antigen 1 positive (Sca-1^{+}) cells have been shown to home more selectively to the retina and to differentiate more often into glial and microglial cells as compared with Sca-1^{-}cells (at 7 days following retinal I/R injury) (Shao et al., 2018). Vascular progenitors from human embryonic stem cells and cord blood-iPSCs were seen to home to and engraft into damaged capillaries within the retina after 45 days in retinas of non-obese diabetic-SCID mice model exposed to I/R, when injected either systemically or into the vitreous (Park et al., 2014). Under I/R conditions, adult rat hippocampus-derived neural stem cells have the potential to migrate to the retinal inner layer within 2 weeks of transplantation. Adult rat hippocampus-derived neural stem cells integrated into the retina and expressed Map2ab, a mature neuron marker, 4 weeks following transplantation (Kurimoto et al., 2001).

Animal studies of stem cells in retinal I/R

The overexpression of heme oxygenase-1 (HO-1) in MSCs using lentivirus significantly decreased hydrogen peroxide-induced retinal injury *in vitro*. HO-1 overexpression reduced ROS levels and apoptosis and induced the activation of anti-apoptotic proteins like Akt and Bcl-2. HO-1 also blocked the activation of pro-apoptotic proteins e.g. cleaved caspase 3 and Bax. MSC-HO-1 treatment also reduced apoptosis and oxidative stress, and prevented retinal thinning and enhanced SOD and CAT activity in a rat retinal I/R model (Li et al., 2017a).

Lineage-negative stem cells transplanted 24 hours after pterygopalatine artery ligation induced retinal I/R injury in mice, were seen to migrate to the retina, where they decreased expression of GFAP, a marker of astrocyte injury and increased expression of two neurotrophic factors BDNF and FGF2, (Minhas et al., 2017). Human bone marrow-derived mesenchymal stem cells (BMSCs) preserved the integrity of the retina in a rat I/R model, where intravitreally BMSC-treated retinas were shown to maintain significantly greater thickness 7 days after injury (Wang et al., 2017). The transplantation of retinal progenitor cells into the subretinal space and superior colliculus also improved electroretinography and visual evoked potentials in a rat retinal I/R model (Li et al., 2014).

The subretinal injection of non-c-Myc iPSC significantly improved electroretinography in the rat retinal I/R model, where stress was induced by elevating intraocular pressure to 110 mmHg for one hour. The non-c-Myc iPSC also improved retinal ganglion cell survival, increased the activity of SOD and CAT, and decreased cellular ROS levels (Fang et al., 2013). The transplantation of bone marrow derived mesenchymal stem cells in the vitreous cavity attenuated the reduction in retinal ganglion cell upon retinal I/R injury in rats. Most of the transplanted cell migrated to the inner limiting membrane where several cells expressed neuron-neuron specific enolase (NSE), neurofilament (NF) and neurotrophic factors including bFGF, BDNF and CNTF. However, in control mice, stem cells were restricted to the vitreous cavity (Li et al., 2009). The intravitreally transplanted adult rat hippocampal progenitor cells (AHPCs) in the elevated intraocular pressure model differentiated under both sets of conditions in normal and injured eyes. However, the morphological integration of AHPCs into the inner retinal layer occurred *only* in the ischemic eyes. Under normal conditions, stem cells were confined to the vitreous inner limiting membrane. Additionally, no functional benefits (assessed by pupil light reflexes and electroretinograms) were observed with AHPCs (Grozdanic et al., 2006).

Summary

The increasing use and acceptance of stem cells in forms of regenerative medicine beyond bone marrow transplants suggest the appropriate application of different types of stem cells in the prophylaxis and treatment of acute and chronic forms of tissue injury resulting from ischemia reperfusion. Among the forms of ischemia reperfusion injury, stem cells have been intensively explored particularly in the settings of ischemic stroke and myocardial infarction where they may both restitute and restore functional and structural components of the heart and brain which have been transiently or permanently injured by ischemic stress. The benefits of stem cell use in other organ systems (kidney, liver) have been successfully demonstrated much more widespread application of stem cells in the treatment of reperfusion in general.

When administered chronically after ischemic episodes, (i.e. after damage has been sustained by target organs), the ability of stem cells to *trans-differentiate* into endothelial cells, neurons and glial support cell lineages which may *restitute* cardiac and brain tissue and promote revascularization, processes which are vital to restoring organ mass and perfusion. However, it also appears true that stem cells acutely release trophic factors (growth factors, exosomes) at and beyond the period of reperfusion which preserves cardiomyocyte, neuronal and stromal components in ischemia-stressed tissues. These processes may limit or prevent initial reperfusion-induced events e.g. apoptosis which drive extensive long-term tissue injury and fibrosis in I/RI. Therefore, stem cells may improve clinical outcomes in I/RI through several different but complementary mechanisms.

Stem cells may therefore represent the ideal 'poly-pill' therapy which could positively influence medical outcomes at several different phases after ischemic stress and through different pathway. Although circulating and bone marrow derived stem cells as well as tissue-resident stem cells share many characteristics which 'cloak' them from the immune system, these different populations of stem cells might be used to confer different types of protection reflecting their anatomic origins, fate potential and the complement of factors they may be able to release.

Additionally, the targeting of stem cell therapeutics, especially in the settings of stroke (via *intra-thecal, intravenous or intraventricular* injection) and in myocardial infarction by intravenous delivery (or even intramuscular injection) might achieve greater and more specific spatial delivery of stem cells to these stressed regions. Future studies which more fully characterize the subtle differences which distinguish different stem cell types may help identify and optimize treatments for ischemic stress and injury and improve outcomes in these devastating forms of tissue destruction.

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