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Podwójna twarz komórek macierzystych w pediatrii: zastosowania terapeutyczne mezenchymalnych komórek macierzystych i zagrożenia rakowymi komórkami macierzystymi

Double face of stem cells in paediatrics: therapeutic applications of mesenchymal stem cells and threats from cancer stem cells

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Streszczenie

Dziesięciolecia badań wykazały, że wiele, jeśli nie wszystkie, w pełni rozwinięte i zróżnicowane narządy i tkanki zawierają subpopulację niezróżnicowanych komórek macierzystych lub progenitorów komórek macierzystych, które w naturalnych lub eksperymentalnych warunkach mogą się odnawiać i różnicować w wyspecjalizowane komórki. Odkrycia te otwierają niezliczone możliwości nowatorskich zastosowań terapeutycznych w leczeniu chorób dorosłych i dzieci. Głównymi źródłami komórek macierzystych stosowanych w terapii pediatrycznej są pępowina i krew pępowinowa, płyn owodniowy, łożysko, szpik kostny, tkanka tłuszczowa, mocz oraz indukowane pluripotencjalne komórki macierzyste, pochodzące z komórek pacjenta. W artykule opisujemy niektóre przykłady zastosowania terapii komórkami macierzystymi w pediatrii. Skupiamy naszą uwagę na terapeutycznych zastosowaniach mezenchymalnych komórek macierzystych w chorobach pediatrycznych. Ważnym, ale negatywnym skutkiem terapii komórkami macierzystymi jest zagrożenie związane z potencjałem onkogennym terapeutycznie stosowanych komórek macierzystych. W pewnych okolicznościach te komórki macierzyste mogą indukować rozwój nowotworów. Ponadto większość nowotworów u pacjentów zarówno dorosłych, jak i pediatrycznych zawiera subpopulację rakowych komórek macierzystych, które są uprzywilejowanymi celami terapeutycznymi w przypadku licznych nowotworów u dzieci. W artykule dokonujemy przeglądu tych dwóch przeciwnych aspektów („podwójnej twarzy") komórek macierzystych w medycynie pediatrycznej i ogólnej.

Słowa kluczowe: mezenchymalne komórki macierzyste (MSC), nowotworowe komórki macierzyste (CSC), terapie komórkami macierzystymi, komórki macierzyste glejaka (GSC), komórki macierzyste białaczki (LSC)

Abstract

Decades of research have shown that many, if not all, fully developed and differentiated organs and tissues contain a subpopulation of undifferentiated stem cells or progenitors of stem cells, which under natural or experimental conditions can self-renew and differentiate into specialised cells. These findings have opened countless possibilities of novel therapeutic applications for the treatment of adult and child diseases. The main sources of stem cells used in paediatric therapies are umbilical cord and umbilical cord blood, amniotic fluid, placenta, bone marrow, adipose tissue, urine, and induced pluripotent stem cells derived from the patient's cells. Here, we describe some of the paediatrically applicable stem cell therapies. We focus our attention on the therapeutic applications of mesenchymal stem cells in paediatric diseases. An important but negative effect of stem cell therapies is the risk of oncogenic potential of therapeutically applied stem cells. Under certain circumstances, these stem cells can lead to tumour development. In addition, the majority of adult and paediatric tumours contain a subpopulation of cancer stem cells which are privileged therapeutic targets for numerous paediatric cancers. In this article, we review these two opposite properties ("double face") of stem cells in general and paediatric medicine.

Keywords: mesenchymal stem cells (MSCs), cancer stem cells (CSCs), stem cells therapies, glioma stem cells (GSCs), leukaemia stem cells (LSCs)

INTRODUCTION

Stem cells are undifferentiated and self-renewing, and have the potential to differentiate into different cell types/tissues. Stem cells are categorised based on their origin and potential functions. **Embryonic stem cells (ESs)** are pluripotent cells in the very early embryo which, during development, differentiate into specialised cells of different tissues[1]. In mammalian (and human) embryos, ESs are present in the inner mass of the blastocyst[2]. **Tissue-specific stem cells**, also called somatic or adult stem cells, are present in different organs and tissues. They have restricted potency in comparison to ESs, being able to differentiate only into the cell types of the tissue/organ they occupy. As such, they are the source of wear and tear, tissue repair, replacement, and regeneration[3]. **Mesenchymal stem cells (MSCs)** are present in the stroma (connective tissue) that surrounds tissues and organs. Their capabilities vary and depend on the place of their origin[4]. **Induced pluripotent stem cells (iPSCs)** are artificially created in the laboratory through the reprogramming of differentiated cells into embryonic-like stem cells[5–7]. The main sources of stem cells used in paediatric therapies are umbilical cord and umbilical cord blood, amniotic fluid, placenta, bone marrow, adipose tissue, urine, and iPSCs derived from the patient's cells[8–10]. Some of these findings have led to the development of cord blood banks that store umbilical cord blood which can be a source of haematopoietic cells for various therapies[11] and new models for the therapeutic testing of paediatric cancers[12].

Another, recently recognised, type of stem cells are **cancer stem cells (CSCs)**, which are located within tumours. Because CSCs are tumourigenic when transplanted into another host, and resistant to conventional anticancer therapies, they are of special interest in the field of cancer therapies[13]. All these different types of stem cells, because of their amazing ability to differentiate into various cell types, replace damaged tissues and organs or promote tumour development, have become invaluable therapeutic tools or targets in different disciplines of modern medicine[14–17]. Because the current literature on stem cells is extremely vast, and exponentially growing, in this review, we will narrow the scope and give just some examples of the applications of stem cells or stem cell-targeted therapies for the treatment of paediatric diseases.

THERAPEUTIC APPLICATION OF MSCs IN PAEDIATRIC DISEASES

The infants who were born prematurely and/or suffer from a chronic multifactorial disorder, hyaline membrane disease (HMD), and received oxygen therapies, may develop a chronic lung disease called bronchopulmonary dysplasia (BPD)[18]. While the majority of patients recover, some are left with a long-term breathing problem[19–25]. Studies show that MSCs therapy is beneficial in the treatment of BPD in rodent models, where it promotes angiogenesis, improve alveolarisation and pulmonary hypertension[25–27]. Data from clinical trials in prematurely born infants at a risk of BPD and children with severe BPD have demonstrated that the umbilical cord-derived MSCs are beneficial[28–30]. Moreover, limited clinical data indicate that transplanted stem cells can be neuroprotective, and may decrease inflammatory injury in preterm neonates, neonatal stroke, and cerebral palsy[31]. However, some studies also show that there are certain subpopulations of MSCs which are myofibroblastic and increase inflammation[29]. Recent studies also indicate that there is a very pronounced effect of the gender of MSCs donor on the effectiveness of the MSCs in PBD therapies. Studies on newborn rats in the hyperoxia-induced PBD model found that the intratracheally applied BM-derived MSCs from female donors were much more effective in decreasing neonatal pulmonary hypertension and vascular remodelling than those from male donors, and showed increased expression of vascular endothelial growth factor (VEGF) and interleukin 10 (IL-10) as well as anti-inflammatory properties[25].

There are also examples of the successful use of MSCs therapy in other areas of paediatrics, such as diabetes[9], pulmonary and cardiac diseases[9,18,32,33], reconstructive surgery and orthopaedy[9,34,35], transplantation, and graft-versus-host diseases[9,36]. One of the examples involves the successful treatment of diabetes mellitus in adolescents aged 14 to 22 years[9,37] with adipose-derived MSCs induced *in vitro* to produce insulin. Another example is that of a 21-month-old child with the bone mineralisation disorder hypophosphatasia who was successfully treated (with the final assessment at 6 years of age) by intravenous delivery of MSCs derived from the sibling's bone marrow[9,38]. A 9-year-old child with graft-versus-host disease developed after bone marrow transplantation was successfully treated (with the final assessment at ~1 year post-transplantation) with MSCs derived from the mother's bone marrow[9,39]. Several clinical trials in children with dilated cardiomyopathy (DCM) that causes paediatric heart failure, also showed a significant improvement of heart function after intramyocardial, intracoronary or peripheral administration of MSCs[9,40–43]. There is also a tremendous need for kidney, bladder and urethra regeneration therapies in children with congenital anomalies. Although there are positive experimental data from animal models, and some promising results of early clinical trials of bladder regeneration using a combination of stem cells and biomaterials in children with neurogenic bladder, which is a neurologic defect associated with spina bifida, so far there are no effective stem cell therapies in paediatric urology[10,44,45].

CSCs – CHALLENGES AND POTENTIAL THERAPIES

Brain cancer in children is one of the most malignant cancers and the leading cause of childhood mortality[46]. Among different cancer types, glioblastoma multiforme (GBM) is the most aggressive and deadly, with an average

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survival between 12 and 18 months[47]. Radiation therapy and various chemotherapies, besides being highly neurotoxic for the developing child's brain[48], are very ineffective because of the presence of CSCs that are resistant, multiply, and result in very aggressive secondary malignancies. CSCs have been shown to be present in various types of paediatric brain tumours including high-grade gliomas (HGGs) and medulloblastomas[49,50]. Paediatric HGGs show the presence of highly resistant glioma stem cells (GSCs), also called glioma initiation or progenitor cells[48], and derived from different mutations[46]. In general, paediatric CSCs have different characteristics than adult CSCs. They differ not only in the expression of different markers but also have unique epigenetic modifications and are regulated by different signalling pathways driving self-renewal than adult CSCs (listed in Tab. 1 in Abou-Antoun et al., 2017[51]). A review of available therapies targeting CSCs suggests that the epigenetic and genetic approaches are the most promising in the treatment of paediatric brain tumours[46,51]. In addition, recent studies show a promising new treatment of paediatric HGGs based on targeting GSCs by the engineered herpes simplex virus (HSV) that is oncolytic for GSCs but harmless for normal cells[48].

Similar considerations are probably also valid for the treatment of paediatric chronic myeloid leukaemia (CML). Recent studies demonstrate that there is a genetic difference between adult and paediatric CML driven by leukaemia stem cells (LSCs) derived from haematopoietic stem cells (HSCs) or committed progenitor cells[52]. The fusion gene *BCR-ABL1* that is present in the CML patients and codes for the chimeric protein with the constitutive tyrosine-kinase activity has a different distribution of breakpoints in paediatric CML than in adult CML[53,54]. This suggests that the *BCR-ABL1*-dependent regulation of oncogenic properties and metastatic behaviour of LSCs, and thus the therapy, ought to be different in the adult and paediatric populations.

Another group of paediatric cancers with high mortality rates are tumours of the connective (mesenchymal or ectodermal) tissue, i.e. sarcomas. They are very heterogeneous, with over 50 known subtypes (listed in Tab. 1 in Dela Cruz, 2013[55]). Recent studies have identified the presence of sarcoma-specific CSCs expressing several distinct markers: pentaspan transmembrane glycoprotein CD133, transmembrane tyrosine kinase growth factor receptor CD117, cell surface protein Stro-1, and human aldehyde hydrogenase ALDH[55]. These findings will contribute to the development of therapies targeting these particular cell populations in paediatric and adult sarcomas.

In summary, there is a tremendous need for further preclinical and clinical studies of existing and novel stem cell therapies, which may help to overcome existing obstacles such as, mentioning just a few, the ethical concerns associated with acquiring stem cells from human embryos, the real and potential tumourigenicity of stem cells, and the restricted proliferative and lineage potential of induced stem cells.

Conflict of interest

The authors do not report any financial or personal affiliations to persons or organisations that could adversely affect the content of or claim to have rights to this publication.

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