Life Sciences 115 (2014) 1–7

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Therapeutic action of bone marrow-derived stem cells against acute kidney injury

Pengfei Liu [a,b,1], Yetong Feng [c,1], Yi Wang [a,*], Yulai Zhou [a,**]

[a] Department of Regeneration Medicine, School of Pharmaceutical Science, Jilin University, Changchun, P.R. China
[b] Key Laboratory of Regenerative Biology, Guangdong Provincial Key Laboratory of Stem Cell and Regenerative Medicine, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, P.R. China
[c] Institute of Human Virology, Zhongshan School of Medicine, Sun Yat-sen University, Guangzhou, P.R. China

ARTICLE INFO

Article history:
Received 6 February 2014
Accepted 20 August 2014
Available online 16 September 2014

Keywords:
acute kidney injury (AKI)
bone marrow-derived mesenchymal stem cells (BMSCs)
kidney repair
kidney regeneration

ABSTRACT

Acute kidney injury (AKI) is a frequent clinical disease with a high morbidity rate and mortality rate, while the treatment options for this intractable disease are limited currently. In recent years, bone marrow-derived mesenchymal stem cells (BMSCs) have been demonstrated to hold an effect therapeutic action against AKI by scientists gradually, and the cells are capable to localize to renal compartments and contribute to kidney regeneration though differentiation or paracrine action. Especially, the advantages of BMSCs, such as low toxicity and side effect as well as autologous transplantation, endue the cell with a promising potential in clinical therapy against AKI. In this review, we mainly provide a concise overview of the application of BMSCs in the treatment of AKI, and summarize a series of published data regarding the mechanisms and optimizations of the BMSC-based therapy in renal repair after AKI. Even though some critical points about the BMSC-based therapy model still need clarification, we hope to develop more reliable pharmacological or biotechnical strategies utilizing the stem cell for the eventual treatment of humans with AKI, based on these studies and the understanding of mechanism of renal protection by BMSCs.

Contents

Introduction

Acute kidney injury (AKI) and its related complications are an important issue of public health all over the world (Bagshaw, 2008; Bussolati et al., 2009; Chertow et al., 2005). The disease is induced by numerous different insults, describes a sudden and prolonged reduction of the renal glomerular filtration rate causing the retention of metabolites (Bussolati et al., 2009), and holds high morbidity and mortality rates (Bagshaw, 2008; Chertow et al., 2005; Kellum and Hoste, 2008). Up to 30% of all patients admitted to intensive care units can be affected by primary or secondary AKI (Tonelli

* Correspondence to: Y. Wang, Department of Regeneration Medicine, School of Pharmaceutical Science, Jilin University, No.1266, Fujin Road, Changchun, P.R. China. Tel.: +86 431 8561 9715.
** Correspondence to: Y. Zhou, Department of Regeneration Medicine, School of Pharmaceutical Science, Jilin University, No.1266, Fujin Road, Changchun, P.R. China. Tel.: +86 431 8561 9299.
E-mail addresses: wangyi@jlu.ecu.cn (Y. Wang), zhouyl@jlu.edu.cn (Y. Zhou).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.lfs.2014.08.025
0024-3205/

et al., 2002). Unfortunately, standard-of-care treatments are not able to modify the course of this disease. Therefore, effective strategies are urgently needed to restore the renal function, as well as to prevent AKI progression. Moreover, the reconstruction of the human injured kidney is more difficult than the regeneration of any other organs, for its complicated anatomical structure and no neonephrogenic zone in renal tissue to form new nephrons (Hopkins et al., 2009).

In recent years, stem cell technology has become the topic of many debates and investigation for its regenerative and potential therapeutic action against AKI and other diseases (Yeagy and Cherqui, 2011), and stem cell-based therapy has been applied in the treatment of many diseases, such as neural disease (Kanno, 2013), diabetes (Wang et al., 2011), and other diseases (Bilousova and Roop, 2013; Daley, 2012; Fujimoto et al., 2012; Li et al., 2013a). For AKI, the therapeutic action of kinds of stem cells in preventing the disease progression and repairing the damaged renal tissues has been demonstrated by several groups, such as hematopoietic progenitor cells (Li et al., 2012), amniotic fluid stem cells (Rota et al., 2012), and kidney-derived mesenchymal stem cells (Choi et al., 2014). In some clinical studies, stem cell technology also has been applied against AKI and other kidney diseases (Humes et al., 2010; Perico et al., 2011; Sengupta et al., 2013). Humes et al. showed that the use of renal progenitor/stem cell therapy could result in effective treatment to improve the dysregulated immunological state as well as the survival of intensive care unit patients with AKI and multiorgan failure in phase II human trials significantly (Humes et al., 2010). Recently, some studies also have applied bone marrow-derived mesenchymal stem cells (BMSCs) in the treatment of AKI in animal models, and their results showed that both renal structure and renal function could be improved with the infusion of BMSCs (Liu et al., 2013c; Qi and Wu, 2013; Reis et al., 2012), and a phase I clinical study has been performed in 16 cardiac surgery patients at high risk of postoperative AKI (NCT00733876) (Togel and Westenfelder, 2012). The patients were treated safely with allogeneic BMSCs in all groups without immune rejection, and preliminary data suggested that BMSCs could protect kidney function and reduce the length of hospitalization and the need for readmission, compared with historical case controls. Another human trial, testing the effects of BMSCs in cisplatin-induced AKI, has been carried out by Mario Negri Institute for Pharmacological Research (NCT01275612) recently. However, the final results have not been published so far, and these early impressions still need further confirmation in adequately powered randomized controlled studies (Rosenberg, 2013).

BMSCs are regarded as an attractive therapy for renal tissue regeneration, as the cells can be isolated from the bone marrow of patients and be modified *in vitro* by vector-mediated gene delivery easily, and they also avoid the ethical ambiguities of using embryonic stem cells (Yeagy and Cherqui, 2011). Besides, the cells are more feasible in autologous treatment than other stem cells, because of their source, number, and safety (Horwitz et al., 2005; Qi and Wu, 2013). In this review, we mainly provide a general overview of the therapeutic action of BMSCs against AKI and discuss strategies in developing BMSC-based therapy for the treatment of AKI in the future.

Therapeutic action of BMSCs against AKI

The stem cells in bone marrow can be classified into hematopoietic stem cells (HSCs) that give rise to all of cells in the hematopoietic system and mesenchymal stem cells (MSCs) that support the hematopoiesis (Lin, 2008). In addition to their function in hematopoiesis, both HSCs and MSCs have been demonstrated to hold the ability to differentiate into many other types of cells *in vivo* or *in vitro*. Before the investigation of BMSCs against AKI, HSCs in bone marrow have been showed to hold therapeutic action against AKI by researchers (Kale et al., 2003; Togel et al., 2004). In 2004, Morigi et al. first demonstrated that BMSCs still hold the function to treat AKI (Morigi et al., 2004). In their study, the injection of BMSCs from male mice remarkably protected cisplatin-treated syngeneic female mice from severe tubular injury and renal function impairment. They also found that BMSCs markedly accelerated tubular proliferation in response to the damage, and Y chromosome-containing cells localized in the context of the tubular epithelial lining and displayed binding sites for Lens culinaris lectin. These results preliminarily indicated that BMSCs not only engraft the damaged kidney, but also differentiate into tubular epithelial cells, thereby restoring the renal structure as well as the function. BMSCs were also compared with HSCs in the evaluation of therapeutic action against AKI, and HSCs failed to exert beneficial effects in some degree. Thus, Morigi's study first demonstrated the possibility that BMSCs could hold the therapeutic action against AKI in preclinical medicine, even in clinical medicine, for their renotropic property and tubular regenerative potential. Later (still in 2004), another group also confirmed the therapeutic action of BMSCs against AKI (Herrera et al., 2004). Differently, in their study, the model of AKI was induced by intramuscle injection of glycerol in C57/BL6 mice, and BMSCs were obtained from the bone marrow of transgenic mice expressing green fluorescent protein (GFP). Anyway, GFP-positive BMSCs injected intravenously could home to the kidney of mice with AKI but not to the kidney of normal mice, and similar to Morigi's study (Morigi et al., 2004), the cells localized in the context of the tubular epithelial lining and expressed cytokeratin, indicating that BMSCs could engraft in the damaged kidney and differentiate into tubular epithelial cells. Taken together, both of the two studies indicated a tropism of BMSCs for the injured kidney and a potential contribution of the stem cells to tubular regeneration as well as to the recovery from AKI.

It has been 10 years since the first report about the therapeutic action of BMSCs against AKI. During this time, the therapeutic action of BMSCs derived from mouse (Herrera et al., 2007; Kim et al., 2013; Liu et al., 2013b), rat (Beiral et al., 2014; Liu et al., 2013e; Yu et al., 2013), rabbit (Xiao et al., 2006; Zhen-Qiang et al., 2012), sheep (Behr et al., 2007), monkey (Moghadasali et al., 2014), even human (Morigi et al., 2008; Tomasoni et al., 2013; Wise et al., 2014), has been demonstrated *in vitro* or *in vivo*, and the model of AKI induced in different kinds of animals (including mouse (Herrera et al., 2007; Kim et al., 2013; Liu et al., 2013b), rat (Beiral et al., 2014; Liu et al., 2013e; Yu et al., 2013), rabbit (Xiao et al., 2006; Zhen-Qiang et al., 2012), sheep (Behr et al., 2007) and monkey (Moghadasali et al., 2014)) with different methods (including ischemia/reperfusion (Kim et al., 2013; Liu et al., 2013b; Wise et al., 2014), cisplatin (Eliopoulos et al., 2011; Gheisari et al., 2012; Xinaris et al., 2013), and so on (Bruno et al., 2009; Herrera et al., 2007; Liu et al., 2013e)) has been applied to confirm the therapeutic action of BMSCs against AKI. The detailed information can be found in Supplementary Table 1. Therefore, the BMSCs have been widely approved to hold the therapeutic function against AKI. In recent years, the major research areas focus on two points, the mechanism and the optimization. Even though the researchers have reached an agreement on the therapeutic action of BMSCs against AKI, there are violent controversies about the major repair mechanism during the process of the treatment with BMSCs. Both differentiation-dependent mechanism (e.g. the differentiation of BMSCs into kidney tubular epithelial cells) and differentiation-independent mechanism (e.g. the paracrine action of BMSCs) have been indicated to exist in the treatment by different groups respectively. Even though which mechanism holds more significant effect against AKI remains in debate, the differentiation-independent mechanism seems to be approved by most scientists. On the other side, scientists still pay much attention on the development of new therapy method to refine the therapeutic action of BMSCs against AKI, such as gene regulation in BMSCs and the treatment of BMSCs with some chemical compounds. We will further discuss the development of the two major research areas (the mechanism and the optimization of BMSC-based therapy against AKI) in recent years respectively.