

Cell based therapies for acute kidney disease



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Introduction

A Global Problem

Kidney disease is a global health problem and one of the largest strains on modern healthcare systems. In particular, Chronic Kidney Disease (CKD) and end-stage renal failure (ESRD) are leading causes of morbidity and mortality amongst OECD countries, and is the 9th leading cause of death in the United States. The European Kidney Health Alliance reports that 1 in 10 EU citizens (approximately 51 million people) has some degree of CKD, and almost 700,000 ESRD patients. The prevalence of kidney disease has increased over the past three decades and if current trends continue these figures are set to double over the course of the next decade.

The cost of treatment of ESRD is significant, transplantation is both the preferred and cheapest treatment. Notably, dialysis treatment can cost up to €80,000 per year per patient and represents currently accounts for 2% of annual healthcare budgets and is predicted to double to 4% in the next 5 years. These figures do not account for other economical costs such as additional medical treatments and reduced life expectancy and capacity to work.

The Kidney and Kidney Disease

Normal kidney function is essential to maintain whole body homeostasis. Its primary functions are to filter metabolic waste from the blood and to regulate the fluid levels in the body. The functional unit of the kidney is the nephron and a typical human kidney is composed of roughly 1 million nephrons and over two dozen specialised cell types. Kidney disease arises

when the renal tissue is damaged to the point where there is a loss of function representing in acute and chronic symptoms.

Acute kidney injury (AKI), previously called acute renal failure (ARF), is a broad clinical syndrome encompassing various etiologies. It is generally defined as an abrupt decrease in kidney function, typically brought on by an event such as blood loss or obstruction of the urinary tract which results in elevated urea and creatinine concentrations in the blood stream. The effects of AKI are commonly reversible, however severe cases can progress to renal failure if left untreated. More recent studies have also shown a link between the occurrence of AKI and the development of more long-term diseases of the kidney. This is thought to arise due the limited regenerative capacity of the kidney tissue which can cause, tissue ischemia, fibrosis, inflammation and tubular dysfunction.

A more severe form of kidney disease, known as chronic kidney disease (CKD) results in the gradual loss of kidney function over time. It is usually caused by a long-term disease such as high-blood pressure or diabetes. This damage is permanent and in severe cases it will progress through several stages to ERSD. If diagnosed early, the progression of CKD can be effectively slowed in the majority of cases through moderate lifestyle changes, however the treatment options for advanced cases are quite limited and invasive.

Treatment Options

Currently the only viable treatment for AKI and CKD is life-long dialysis treatment, and while dialysis can lead to drastic improvements in renal filtration, it is not capable of replacing many of the other important functions

of the kidney such as vitamin D activation and hormone release.

Consequently, patients undertaking long-term dialysis treatment frequently suffer further degeneration of their kidney function, higher mortality rates and an overall lower quality of life. If AKI and CKD develop into ESRD the only viable treatment is orthotopic transplantation. However, this presents a number of concerns and challenges. Primarily, the supply of donor kidneys is approximately 1/5th the demand. Despite the required life-long use of immune-suppressants post operation, 40% of recipients will reject the donor organ and face a life-expectancy of just 10 years. Recent developments in the fields of tissue engineering and regenerative medicine show promise in addressing some of the above concerns. The purpose of this paper is to review current developments in cell-based therapies for the treatment of kidney disease.

Reword above.

Overview of Regenerative Medicine for the treatment of Kidney Disease

Recent developments in the areas of tissue engineering and cell-based methodologies have led to the generation of novel regenerative medicine techniques which are showing promise in addressing some of the above concerns and offer potential treatment options for both kidney disease and ESRD. While there are a number of regenerative medicine approaches being pursued, two are showing the most promising advances in repairing and restoring kidney function. In particular several purely cell-based therapies using primary renal cells and stem cells are currently under clinical trial.

However, when kidney disease progresses to more severe states, the degenerating kidney tissue needs to be fully or partially replaced. Progress in 3D cell culture methods has enabled the production of functional 3D functional renal structures in vitro which can then be implanted, however their clinical application remains challenging. Although the research is only in its infancy Decellurisation / Recellurisation strategies for whole organ replacement shows promise for patients suffering from ESRD and this would replace the need for organ donors.

Summary

Kidney disease is a significant global health problem which places a large strain on modern healthcare systems, and a leading cause of death throughout the developed world. It presents as a broad clinical syndrome with few viable treatment options, none of which can fully restore a patient's kidney function or health status. Recent developments in tissue engineering and cell-based methodologies have led to the generation of more successful treatment options. Tissue engineering strategies have the potential to produce and replace entire organs including the kidney, however these strategies are encountering a number of problems and are unlikely to see clinical application in the medium term. A number of cell-based treatment methodologies have been developed which are showing promise in the treatment of kidney disease. For this reason, the focus of this report will be to review cell therapy treatments for acute kidney injury.

Experimental and Technical details

Introduction

There are two primary challenges which are encountered in the development of cell-based therapies for the treatment of AKI. The first problem relates to the diversity of illnesses / causes which can result in AKI, for example it may arise as a result of severe dehydration or due to the heart pumping out less blood after a heart attack. Each of these causes can often be characterised by a variety of disease specific damage to tissue. This issue is compounded by the second problem encountered in the development of cell-based treatments for AKI, which is the highly complex structure of the kidney. The most common causes of AKI are transient and prolonged renal hypoperfusion, both of which result in alterations to multiple components of the kidney, including tubules, glomeruli, vessels and interstitium (Devarajan P., 2006), (Patschan, D et al., 2016). The number of tissue types and cellular processes involved in AKI are unlikely to be addressed by a single cell source.

Despite these challenges a number of attempts have been made to derive a cell-based therapy for the treatment of AKI, which have culminated in the initiation of several human studies. This report will first look at the different approaches being used by examining the different stem cell populations being utilized. The approaches will then be compared and the most promising selected for further examination. It has been decided to examine the following cell populations in this report: induced Pluripotent Stem Cells (iPSCs), Spermatagonial Stem Cells (SSCs), Proangiogenic Cells (PACs) and

Endothelial Colony Forming Cells (ECFCs), and Mesenchymal Stem Cells (MSCs).

Induced Pluripotent Stem Cells

Both embryonic and adult stem cells have pluripotent abilities, however adult stem cells do not have the capability to adequately treat AKI and the use of embryonic stem cells often encounters ethical problems. However, the 2012 Nobel prize for medicine was awarded for “ the discovery that mature cells can be reprogrammed to become pluripotent”. These induced pluripotent stem cells (iPSCs) are derived from a patient’s own tissue and are capable of regenerating whole tissue, which is particularly applicable to organs such as the kidney which lack substantial regenerative capacity (Morales et Wingert, 2014)

The most common method of generating iPSCs from patient somatic cells is through the use of viral vectors to express the necessary reprogramming factors. Typically, integrative viral vectors transduce the required genetic material by incorporating itself into the patient’s genome however this can often lead to problems of cell death, residual expression and re-activation of reprogramming factors, immunogenicity, and mutagenesis (Zhao et al., 2011). An alternative method to address some of these concerns has been developed which generates iPSCs through the use of non-integrative viral vectors. The genetic material of non-integrating vectors, in contrast, remains in the cytoplasm. The advantage of this method is that there is limited potential to interfere with essential cell genes, however a particular drawback is that expression of reprogramming factors is transient and is lost upon mitosis. Although mice models have shown iPSCs promise in the <https://assignbuster.com/cell-based-therapies-for-acute-kidney-disease/>

treatment of AKI, significant questions still need to be addressed as to their safety in a clinical setting due to the use of viral material.

Spermatogonial Stem Cells

Spermatogonial stem cells (SSCs) are a unipotent cell line found in the male testes and are precursors for spermatocytes (De Rooij, 2017). While this may be a unipotent cell line under normal conditions, recent experiments have discovered their ability to spontaneously convert to embryonic like stem cells, Germline cell-derived Pluripotent Stem Cells, (GPSCs) if cultured under the correct conditions. Two culture methods have been reported to reprogram spermatogonial stem cells from adult male mouse testes, one requires the SSCs be cultured in a medium containing leukemia inhibitory factor, the other involves co-culturing Mitomycin-C treated embryonic fibroblasts from mice with SSCs. (De Chiara et al., 2014) The ability of these mouse cell lines to be cultured long term as well as differentiate into various renal cells has been demonstrated and has promising potential for the treatment of AKI (Wu et al, 2008).

More recent investigations into human SSCs have confirmed their ability to spontaneously differentiate into embryonic cells, given the right conditions. These cells can also differentiate into the three primary germ lines without the formation of large teratomas (Kossack et al., 2009). The ability to be reprogrammed without the use of reprogramming factors and to not form large teratomas addresses many of the limitations / challenges associated with iPSCs and offers a promising potential treatment option for AKI. However, research into the use of SSC cultures for the treatment of AKI is

limited and many more studies will be required to confirm its potential and efficacy.

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are a multipotent cell population, meaning they can differentiate into a number of cell types but not every cell type. They are isolated from bone marrow, umbilical cord tissue, adipose tissue and a number of other sources. In comparison to both embryonic stem cells and induced pluripotent stem cells, MSCs are very easily cultured and expanded in vitro and have a great capacity for self-renewal while maintaining their multipotency. MSCs can be readily directed to differentiate into a specific cell type by culturing under defined conditions (Ankrum et al., 2014).

MSCs have been shown to demonstrate a number of immunomodulatory effects, which can reduce inflammation and regulate the immune system. This has made it a popular choice for the development of cell-based therapies and in particular for treatments of acute kidney injury. Studies have also shown that MSCs which have been injected intravenously have the ability to seek out the damaged inflamed sites of a tissue (Devine et al, 2001), this offers an alternative to direct injection to the injured site. It is for many of the above reasons that MSCs are the cell-line which has received the most attention in the development of cell-based therapies.

Proangiogenic Cells and Endothelial Colony Forming Cells

Proangiogenic Cells (PACs) and Endothelial Colony Forming Cells (ECFCs)

Comparison of Stem Cell Types

Over the past number of years, a significant body of research has been produced on the topic of cell-based treatments for acute kidney injury. In the development of these therapies four types of stem cells have shown the most potential, induced Pluripotent Stem Cells (iPSCs), Spermatagonial Stem Cells (SSCs), Proangiogenic Cells (PACs) and Endothelial Colony Forming Cells (ECFCs), and Mesenchymal Stem Cells (MSCs). An outline of each stem cell type was provided above along with a general summary of their current development status. iPSCs can differentiate into any cell type and can be easily produced from a number of cell types, facilitating a non-invasive cell harvest procedure, and as a result are showing particular promise for the generation of a potential treatment. However, a number of technical challenges are currently holding this cell type back from clinical applications, these include the formation of large teratomas as well as the current requirement to use the oncogene c-Myc in the reprogramming process to produce iPSCs. This particular oncogene has been linked with tumour formation and its introduction to a patient poses a health risk.

SSCs have been able to address many of the above shortcomings associated with iPSCs. Most notably they do not require the use of the c-Myc oncogene or viral vectors in their reprogramming process. These cells can also differentiate into the three primary germ lines without the formation of large teratomas and can be cultured for a significant length of time without a decline in cell quality. However, while studies have shown the ability of SSCs to differentiate into a number of renal cell types, there is a limited amount of data on its efficacy for the treatment of acute kidney injury in humans. While

both male and female patients can benefit from potential SSCs based treatments, the cells can only be harvested from male donors in what is a particularly invasive cell harvesting procedure.

MSC based therapies have demonstrated a number of properties which demonstrate its suitability for the treatment of acute kidney injury. In particular it has shown a number of immunomodulatory effects and an ability to be easily cultured and expanded in-vitro. While the predominant source is MSCs is bone marrow, a number of other cell sources such as adipose tissue, which would require a much less invasive cell harvesting procedure, have been shown to be viable.

While all four cell types have demonstrated potential for the development of therapies for AKI, there is a lack of data currently available on the use of iPSCs, SSCs and ECFS to warrant further investigation in this report. Taking this into consideration, the remainder of this report will focus on MSC based therapies for the treatment of AKI.

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