Stem Cell Therapy in Acute Renal Failure in Rats

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Abstract

One of the major causes of death is acute renal failure. The hemodialysis was the only way of treatment. The aim of our study was to evaluate the therapeutic value of mesenchymal stem cells and hepatocyte growth factor (HGF) as an alternative treatment and prediction of their mechanism of action through the measurement of TNF-α, IL-10 & VEGF. Our results showed that mesenchymal stem cells & HGF can be used effectively as a way of treatment.

Key Words:

Mesenchymal stem cells

TNF-α

IL-10

VEGF

HGF

Acute renal failure

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List of abbreviations

ARF	Acute renal failure
ACEI	Angiotensin converting enzyme inhibitor
ANCA	Antinuclear antibody
ARB	Angiotensin receptor blocker inhibitor
ATN	Acute tubular necrosis
ATP	adenosine triphosphate
bFGF	basic fibroblast growth factor
BIO	6-bromoindirubin-3'-oxime
BM	bone marrow
BMDC	bone marrow–derived cells
BMSC	bone marrow stem cell
BPH	benign prostatic hypertrophy
BUN	Blood urea nitrogen
CD	Cluster of differentiation
CFU-F	fibroblastoid colony forming unit
CRRT	continuous renal replacement therapy
CVVH	continuous veno-veno-hemofiltration
DIC	Disseminated intravascular coagulopathy
DNA	Deoxyribonucleic acid
ECM	extracellular matrix
EGF	epithelial growth factor
ESC	embryonic stem cells
FENa	fractional excretion of sodium
G_0/G_1	Gap note/Gap 1 phase
GBM	glomerular basement membrane
GCSF	granulocyte-colony stimulating factor
GFP	green fluorescence protein
GFR	glomerular filtration rate

GIT	Gastro intestinal tract
GM-SCF	granulocyte-macrophagecolony-stimulating factor
GN	glomerulonephritis
GTC	guanidine thiocyanate
GVHD	graft-versus-host-disease
H&E	haematoxylin and eosine
H-CAM	homing-associated cellular adhesion molecule
HGF	hepatocyte growth factor
HSC	hematopoietic stem cell
HUS	hemolytic uremic syndrome
I/R	ischemia-reperfusion
ICM	inner cell mass
ICU	intensive care units
IHD	intermittent hemodialysis
IL	Inter leukin
IM	intermediate mesoderm
kD	Kilo Dalton
LFA-1	lymphocyte function–associated antigen 1
MAPC	multipotent adult progenitor cell
MET	mesenchyme-to-epithelial
MM	metanephric mesenchyme
MMP	matrix metalloproteinase
MSC	mesenchymal stem cell
MT	masson trichrome
MT1	membrane type 1
NGAL	neutrophil-gelatinase-associated lipocalin
NK	Natural killer cells
NSAID	Non steroidal anti-inflammatory drug
OI	osteogenesis imperfecta
P value	Probability value

PAS	periodic acid shift
PCR	Polymerase chain reaction
PDGF	platelet derived growth factor
PG	prostaglandin
RBC	Red blood corpuscles
RT-PCR	Reverse transcriptase PCR
SCF	stem cell factor
SCNT	somatic cell nuclear transfer
SD	Standard deviation
SDF-1	stromal-derived factor 1
TGF-β	transforming growth factor-β
THP	Tamm-Horsfall protein
TNF-α	Tumor necrosis factor-α
UB	ureteric bud
UCB	umbilical cord blood
VCAM-1	vascular cell adhesion molecule
VEGF	Vascular endothelial growth factor
VLA-4/5	very late antigen 4/5

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Introduction

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Introduction

Acute renal failure (ARF), also known as acute kidney injury, is a rapid loss of renal functions due to damage to the kidneys, resulting in retention of the nitrogenous compounds (urea and creatinine) and non nitrogenous waste products that are normally excreted in urine **(Albright RC Jr, 2001).**

Depending on the severity and duration of renal dysfunction, this accumulation is accompanied by metabolic disturbances, such as metabolic acidosis and hyperkalemia, changes in body fluid balance, and effects on many other organ systems. It can be characterized by oliguria or anuria **(Singri N et al, 2003).** It is a serious disease and treated as medical emergency.

Causes of acute renal failure are

1- Pre renal causes such as hypovolaemia usually from shock or dehydration, vascular problems such as renal vein thrombosis, atheroembolic disease or prolonged ischemia of the kidneys due to vascular injuries during surgery.

2- Renal causes such as prolonged use of certain medications such as non steroidal anti-inflammatory drugs as aspirin and antibiotics as aminoglycosides, autoimmune diseases that affect the kidney as glomerulonephritis and systemic lupus erythematosus, multiple myeloma and hemolytic uraemic syndrome, chronic diseases such as chronic uncontrolled hypertension and chronic uncontrolled diabetes mellitus.

3- Post renal causes such as prostatic cancer and kidney stones. **(Star RA, 1998).**

Acute renal failure is present in 1 to 5 percent of patients at hospital admission. The condition affects 15 to 20 percent of patients in intensive care units (ICUs); reported mortality rates range from 50 to 70 percent in those patients **(Albright RC Jr et al, 2001).** Infection and cardiorespiratory complications are the most common causes of death in patients with acute renal failure.

In clinical practice, ischemia-reperfusion (I/R) injury is the most common cause for acute renal failure. The pathogenic events in ischemia/reperfusion injury include acute tubular necrosis, apoptosis, glomerular injury and inflammation.

Management of acute renal failure depends first on correction of the metabolic abnormalities like the correction of hyperkalemia and correction of metabolic acidosis then treatment of the cause as correction of the hypovolemic state during shock or immunosuppressive therapy for glomerulonephritis (**Kodner CM & Kudrimoti A, 2003).** Although a number of agents and growth factors have been proven effective in the amelioration of ARF in otherwise healthy animals, no significantly effective new therapy has been introduced into clinical practice in decades. It is for these reasons that fundamentally new strategies for the treatment of ARF are needed.

Stem cell therapy holds a great promise for the repair of injured tissues and organs, including the kidney. Stem cells are undifferentiated cells that undergo both self-renewal and differentiation into one or more cell types **(Weissman IL, 2000),** & are found in adult and embryonic tissues and have potential uses in therapies designed to repair and

regenerate organs. There has been considerable focus on the ability of stem cells to differentiate into non-haematopoietic cells of various tissue lineages, including cells of the kidney **(Oswald J et al 2004).** This growing evidence has led to a reconsideration of the source of cells contributing to renal repair following injury.

The mechanism of action of stem cell therapy is unclear in most disease conditions. Very-low-level organ engraftment of circulating bone marrow-derived stem cells has been shown **(Orlic D et al, 2001)** but was not corroborated by others **(Balsam LB et al, 2004).** The percentage of incorporated stem cells varies widely, but it is usually below 1% in a given organ, and, in addition, its magnitude depends on the studied disease model. Other mechanistic possibilities for the therapeutic effects of stem cells include fusion with resident organ cells **(Wurmser AE & Gage FH, 2002)**, immunomodulation **(Aggarwal S & Pittenger MF, 2005)** and paracrine mechanisms elicited through trophic mediators **(Caplan AI & Dennis JE, 2006)** that result in the inhibition of fibrosis and apoptosis, enhancement of angiogenesis, stimulation of mitosis, and proliferation and differentiation of organ-intrinsic precursor or stem cells.

Hepatocyte growth factor (HGF), first identified **by Russell WE et al, 1984** then purified and cloned **by Nakamura T et al, 1986** as a potent mitogen for fully differentiated hepatocytes.

Hepatocyte growth factor exerts mitogenic responses in renal epithelial cells derived from distinct regions and species, including rabbit and rat proximal tubular cells **(Harris RC et al, 1993)** and rat glomerular epithelial cells. HGF stimulates the proliferation of renal epithelial cell lines, including a rat visceral glomerular cell line **(Kawaguchi M et al, 1994),** proximal tubular cell lines **(Ishibashi K et al, 1992)**. Likewise,