STEM CELLS AND THEIR ROLE IN THE TREATMENT OF PEDIATRIC CARDIAC FAILURE

Essay

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14C:	14Carbon
AAV:	adenoassociated virus
ABCG2:	ATP-binding cassette subfamily G member 2
AC:	adenylate cyclase
ACEI:	angiotensin-converting enzyme inhibitor
AdV:	adenovirus
Akt:	a serine threonine kinase
ALL:	acute lymphocytic Leukemia
AML:	acute Myelocytic Leukemia
ANP:	atrial natriuretic peptide
AR:	adrenergic receptor
ARB:	angiotensin-receptor blocker
ASTAMI:	autologous Stem Cell Transplantation in Acute Myocardial Infarction
ATP:	adenosine triphosphate
BAF:	barrier-to-autointegration
Bcl-2:	B-cell lymphoma 2 (antiapoptotic gene)
Bcl-XL:	B-cell lymphoma XL (antiapoptotic gene)
bFGF:	basic fibroblast growth factor
BM:	bone marrow

BMC: bone marrow cell

BMMNC: bone marrow mononuclear cell

BMP: bone marrow morphogenic protein

BMT: Bone marrow transplant

BNP: brain natriuretic peptide

BOOST: bone marrow transfer to enhance ST-elevation infarct regeneration

CAD: coronary artery disease

cAMP: cyclic adenosine monophosphate

CBEs: cord-blood-derived embryonic-like stem cells

CCS: Canadian Cardiovascular Society

CDC: Cardiosphere derived cardiomyocyte

CHDs: congenital heart defects

c-Met: mesenchymal epithelial transition factor

CML: Chronic Myelocytic Leukemia

CMs: cardiomyocytes

CPC: cardiac progenitor cell

CRT: cardiac resynchronization therapy

CSC: cardiac stem cell

CT-1: cardiotrophin-1

CUPID: Calcium-Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Disease

EC: excitation contraction

ECC: early committed cell

EcSOD: extracellular superoxide dismutase

EF: ejection fraction

eGFP: enhanced green fluorescent protein

EndMT: endothelial–mesenchymal transition

EPC: endothelial progenitor cell

ERK: extracellular signal-regulated protein kinase

ESC: embryonic stem cell

Eur.Ph: European Pharmacopoeia

FGF: fibroblast growth factor

GATA: guanine-adenine-thymine-adenine

G-CSF: Granulocyte colony-stimulating factor

GFP: green fluorescent protein

GH: growth hormone

GRK: G protein–coupled receptor kinase

GRO: growth-related oncogene

GVHD: Graft versus host disease

H2S: hydrogen sulfide

hBMSCs: human BM-derived multipotent stem cells

HBsAg: Hepatitis B surface antigen

HBVcAb: Hepatitis B virus core anti body

HCPCs: human cardiac progenitor cells

hEBs: human embryoid bodies

HEPA: High Efficiency Particulate Absorbing

HEPA: high efficiency particulate air

hESCs: Human embryonic stem cells

HF: heart failure

HGF: hepatocyte growth factor

HIF:	hypoxia-inducible factor
HMGB:	high-mobility group box protein
HO-1:	heme-oxygenase 1
hSC:	hematopoietic stem cell
human 50:	Human Fibroblast Growth Factor-basic (rHuFGF-b) 50 μg
ICD:	intracardiac defibrillator
ICM:	inner cell mass
IGF:	insulin-like growth factor
IGF-1R:	insulin-like growth factor 1 receptor
IL:	interleukins
iN:	induced neurons
IP:	inhibitor protein
iPS:	induced pluripotent stem
KAT:	Kupio Angiogenesis Trial
KO:	knockout
LAD:	left anterior descending coronary artery
LIF:	leukemia inhibitory factor
LV:	left ventricle
LVAD:	left ventricular assist device
MAPCs:	multipotent adult progenitor cells
MCP:	monocyte chemoattractant protein
Mef2c:	myocyte enhancer factor-2c
MEFs:	mouse embryonic fibroblasts
mESCs:	mouse embryonic stem cells
MI:	myocardial infarction

MIAMI:	marrow-isolated adult multilineage inducible
miR:	microRNA
MLC:	myosin light chain
MPT:	mitochondrial permeability transition
MSCs:	Mesenchymal stem/stromal cells
MSCs:	Myocardial stem cells
MVO2:	myocardial oxygen consumption
NO:	nitrous oxide
NO2−:	nitrite
NOD/scid:	nonobese diabetic/severe combined immunodeficiency
NOS:	nitrous oxide synthase
NYHA:	The New York Heart Association
PAA:	polyacrylic acid
PBSCs:	Peripheral Blood Stem Cell Separation
PCR:	Polymerase chain reaction
PEO:	polyethylene oxide
PKA:	protein kinase 1
PLGA:	Poly lactic-co-glycolic acid
PLN:	phospholamban
PP1:	protein phosphatase 1
PTIO:	2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidazole-1-oxyl 3-oxide
PVA:	polyvinyl alcohol

REPAIR-AMI: Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction

ROS: reactive oxygen species

RyR: ryanodine receptor

Sca-1: stem cell antigen-1

SCID: Severe combined immunodeficiency disease

SDF: stromal-derived growth factor

SERCA2a: SR Ca2+ ATPase in the myocytes

SOPs: Standard Operating Procedures

SP: side population

SR: sarcoplasmic reticulum

STEMI: ST-elevation acute myocardial infarction

TAC: transaortic constriction

Tbx5: T-box transcription factor-5

TGF: transforming growth factor

TNF: tumor necrosis factor

TOPCARE-AMI: Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction

TOPCARE-CHD: Transplantation of Progenitor Cells and Recovery of LV Function in Patients with Chronic Ischemic Heart Disease

UCB: umbilical cord blood

USP: United States Pharmacopeia

VEGF: vascular endothelial growth factor

VOD: Veno-occlusive disease

Introduction

Based on strong research evidence, pediatric Heart failure (HF) is a clinical syndrome that occurs when cardiac output is not sufficient to meet the metabolic demands of the body. Strong research evidence suggests that although there are many specific causes of HF, only a few primary mechanisms operate in all patients regardless of age (volume loading, afterload stress, disorders of rhythm, and impaired myocardial contractility) (Kay et al., 2001).

The medical therapies for managing HF, including blockade of the sympathetic nervous system, afterload reduction with vasodilators, and treatment of cachexogenic pathways were pioneered in adults and have not been well studied in children. Most pediatric HF treatments depend on experience and reason rather than on evidence-based studies in infants and children (Moffett et al., 2006).

Surgical and other interventional therapies to correct the anatomic problems leading to heart failure in congenital heart disease will continue to be refined. Cell-based therapy has been gaining increasing prominence for cardiovascular diseases in adults but has received little attention in pediatrics. Potential indications for stem cell use in pediatric heart failure include repair of ventricular myocardium and creation of biological heart valves, tissue-engineered vessels, and biological pacemakers (Pillekamp et al., 2008).

In man, the rate of cardiomyocyte renewal has been estimated as 0.06% per day, so that rebuilding of the whole heart should take 4–5 years (Anversa et al., 2006). Other estimates of the cardiomyocyte cell cycle activity range between 0.0005 and 3%. It is well known, however, that the cardiac parenchyma destroyed during an ischemic accident does not regenerate spontaneously. During the so-called remodelling, it is replaced instead by a scar of fibrous tissue, suggesting that the cardiac stem cell (CSC) potential is not enough for significant repair (Rubart et al., 2006).

The whole heart must be renewed within less than 1 year (Sanchez et al., 2005).

Stem cells are defined as unspecialized or undifferentiated precursor cells with the capacity for self-renewal and the power to differentiate into multiple different specialized cell types. Grossly, stem cells are divided into either embryonic stem cells (ESCs) or adult stem cells, with adult stem cells being further divided into specific tissue stem cells, umbilical stem cells, or bone marrow stem cells. Adult stem cells are certainly the most commonly studied, as embryonic stem cells (ESCs) are present only during fetal development (Nagy et al., 2005).

In 1998, James Thompson and his colleagues reported the establishment of human ESC lines that were extracted from embryos created by in-vitro fertilization. These cells, which form the inner cell mass at day 5−7 after fertilization, were transferred to a culture dish with feeder cells and allowed to replicate. In theory, these cells could retain their self-renewing