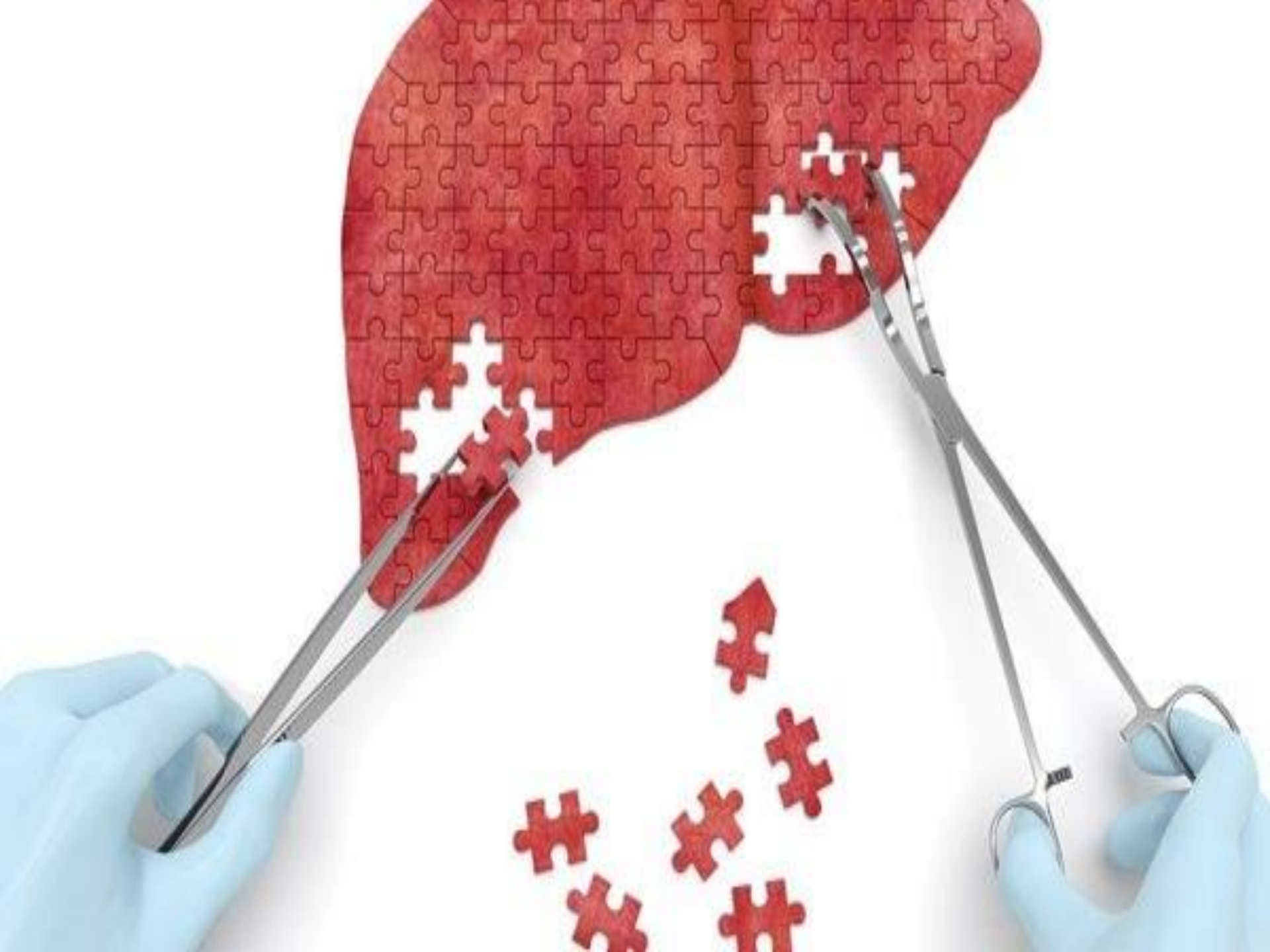
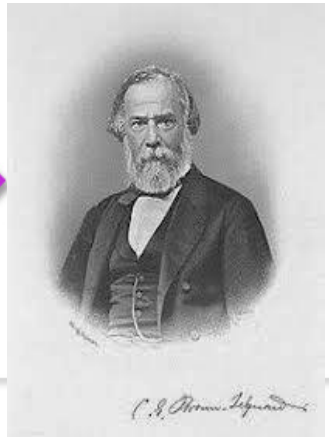


دانشگاه علوم پزشکی
و خدمات بهداشتی درمانی تهران

Perspective of placenta derived mesenchymal stem cells in acute liver failure



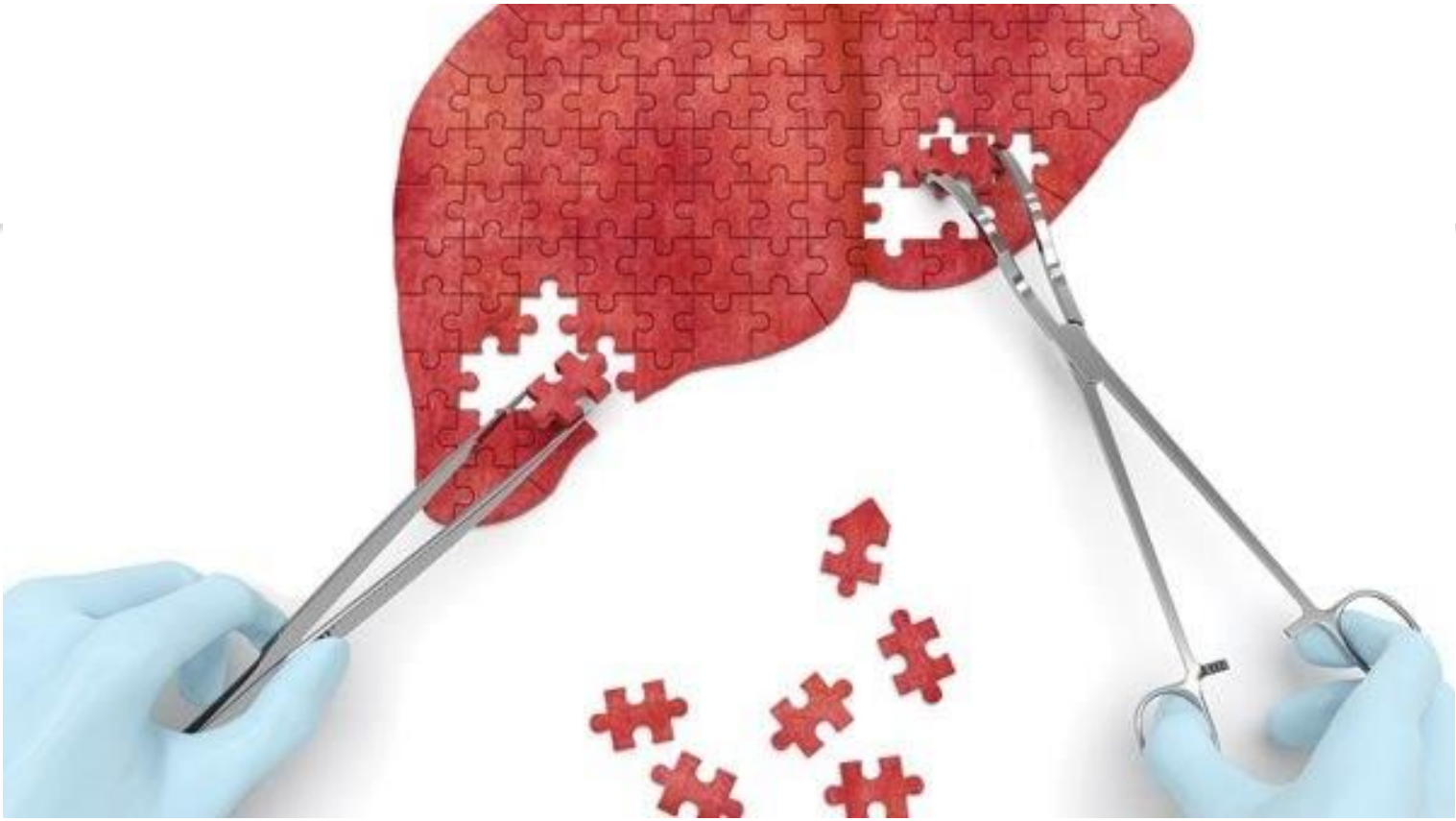
Cell Therapy

History of cell replacement therapy

- 19th century - **Charles-Édouard Brown-Séquard** (1817–1894) injected animal testicle extracts in an attempt to stop the effects of aging
- 1931 - **Paul Niehans** (1882–1971) – **inventor of cell therapy** – attempted to cure a patient by injecting material from calf embryos
  - Niehans claimed to have treated many people for cancer using this technique, though his claims have never been validated by research
- 1953 - laboratory animals could be helped not to reject organ transplants by pre-inoculating them with cells from donor animals
- **1968** - in Minnesota - **first successful human bone marrow transplantation**
  -Till today, the cell replacement therapy is most advanced with
- **1998 – first isolated human embryonic stem cells** – great leap in research
- **2006 – first Induced Pluripotent Cells** - revolution to the field

Cell Therapy". American Cancer Society. November 2008. Retrieved 15 September 2013.

Berche, P. (2010). "La thérapeutique du docteur Brown-Séquard". *Annales d'Endocrinologie*. **71** (2): 69 75. doi:10.1016/j.ando.2010.01.003



Acute liver failure

Acute liver failure

- An unpredictable and potentially catastrophic condition
- More than 2500 cases each year in the United States.

- ALF:Hepatocellular disorders such as coagulopathy and encephalopathy with INR≥1.5 in patients without a history of liver disease within 26 weeks.

- http://www.aasld.org/practiceguidelines/Documents/AcuteLiverFailureUpdate2011.pdf (Accessed on August 08, 2012).
- Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. Hepatology 2012; 55:965.

Acute liver failure

- More than half of the cases of ALF progression require liver transplantation and significant improvements have been reported in the last decade after liver transplantation.

- The three main factors determining the prognosis of this disease :
  - metabolic problems leading to the loss of liver cells
  - secretion of toxins and mediators from the liver tissue
  - capacity of the remaining hepatocytes to repair the liver.

Common treatments

- ICU care
- Hydration
- N-acetylcysteine
- FFP and platelet administration
- Glucose
- Stress ulcer prophylaxis
- Broad-spectrum antibiotics
- Vasoconstrictors
- Dialysis
- ….

Etiology of ALF

Table 1 Causes of ALF in adults

Cause of ALF	Frequency (%)
Acetaminophen overdose	47
Viral Hepatitis	10
Drug-induced liver injury	11
Autoimmune hepatitis	5
Ischemia	4
Wilson's disease	2
Indeterminate causes	14
Other	7

Abbreviation: ALF, acute liver failure.

Immune system in patients with ALF

- Impaired function of both humoral and innate immunity is implicated in the pathophysiology of ALF.

- Begins with necrosis of hepatocytes.

- Oxidative stress results in the production of reactive oxygen species, which in turn activates the Janus kinase (JNK) signaling pathway.

Immune system in patients with ALF

- DAMPs (Damage associsted molecular pattern)
  - activate hepatic macrophages (Kupffer cells (KCs)) and induce the formation of inflammasome.
  - Leads to the secretion of IL-1, IL-18, and caspase 1
  - DAMPs are detected by Kupffer cells that express a large number of DAMP receptors, including TLR4, TLR9, and RAGE.
  - KCs are activated in this process and release inflammatory cytokines such as TNFα, oxygen radicals, and chemokines such as CCL2 under the effect of inflammatory signals.
  - Neutrophils and monocytes recruitment and thereby increases inflammation

Immune system in patients with ALF

- The liver cell injury leads to the release of inflammatory mediators such as DAMPS, TNFα, IL-6, and IL-18
- Inflammatory cells such as lymphocytes and monocytes reach the damage site and enhance the inflammatory response.
- Coagulation factors as well as primary and secondary homeostasis also become involved and result in SIRS reaction.
- These reactions are associated with the development of HE ,bacteremia and, in some cases, infection .

Hepatic encephalopathy in ALF

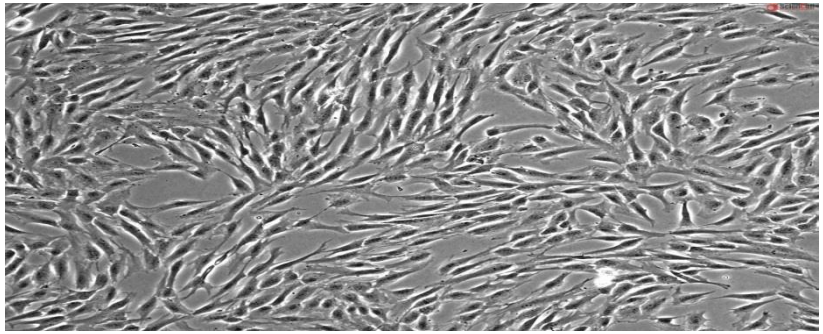
- Compensatory anti-inflammatory response syndrome (CARS) occurs in reaction to SIRS, leading to the secretion of anti inflammatory factors (including IL-10 and SPLI) from hepatic macrophages during the early stages.

- Both of these reactions eventually lead to dysregulation of the immune system and defective immune responses to microbial agents.

Hepatic encephalopathy in ALF

- Hepatic encephalopathy (HE) is a function of neurotoxins that reach the brain through the bloodstream.

- Various factors such as blood ammonia levels, infection, necrotic liver, toxins, and systemic inflammatory response syndrome (SIRS) can lead to HE.



Mesenchymal stem cells

- MSCs are fusiform non-hematopoietic cells capable of adhering to plastic surfaces, which can be isolated from various tissues, including placenta, umbilical cord, bone marrow, adipose, and other tissues.
- MSCs have different regeneration potentials, which is due to the microenvironment and cellular niches affecting their fate.

- The definition of MSCs according to International Society for Cell Therapy (ISCT) is as follows: MSCs are

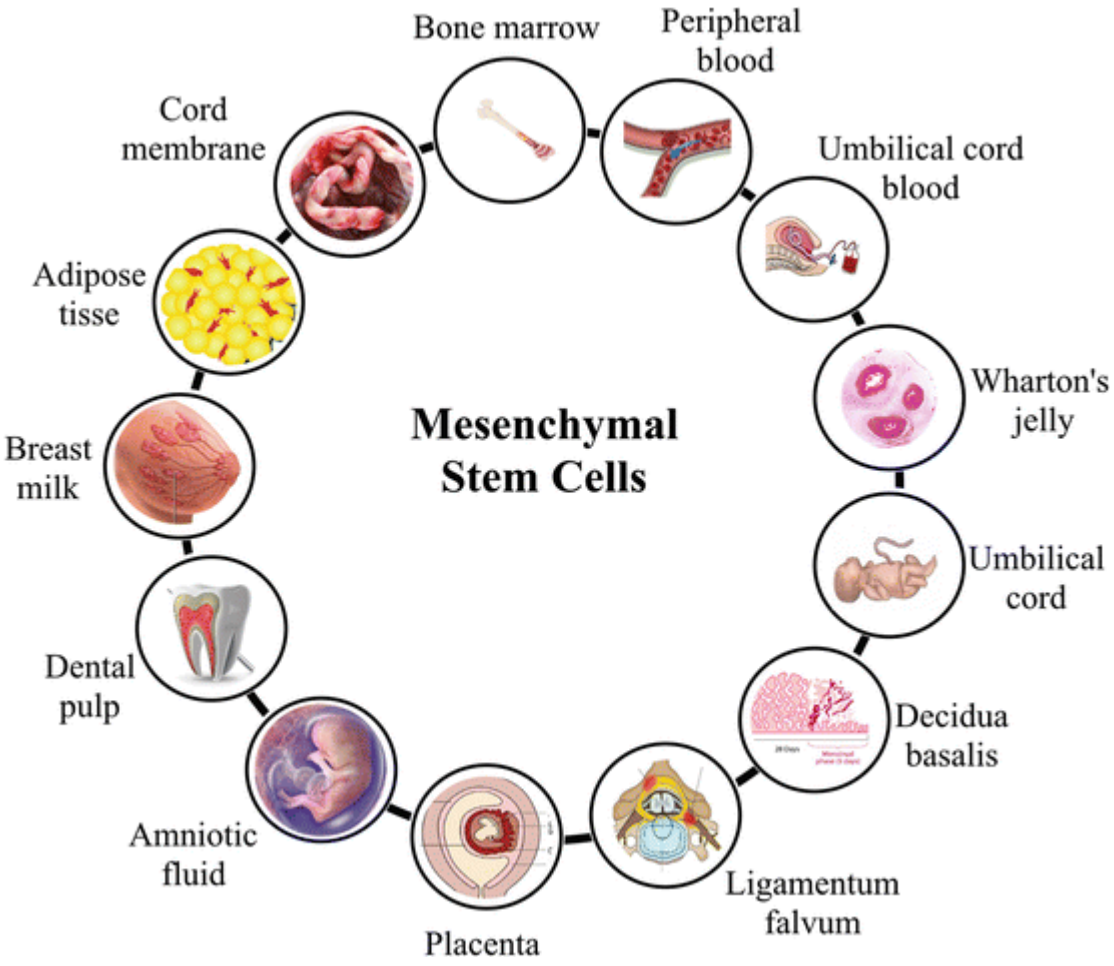
(1) able to bind plastic surfaces,

(2) able to differentiate into all three classes of chondrocytes, adipocytes and osteocytes in vitro, and

(3) capable of expressing CD73, CD90, and CD105 markers but not hematopoietic markers like CD45, CD14, CD19, CD34, and HLADR

Samsonraj RM, Concise review: multifaceted characterization of human mesenchymal stem cells for use in regenerative medicine, 2017.

Mesenchymal stem cells



MSCs release numerous factors

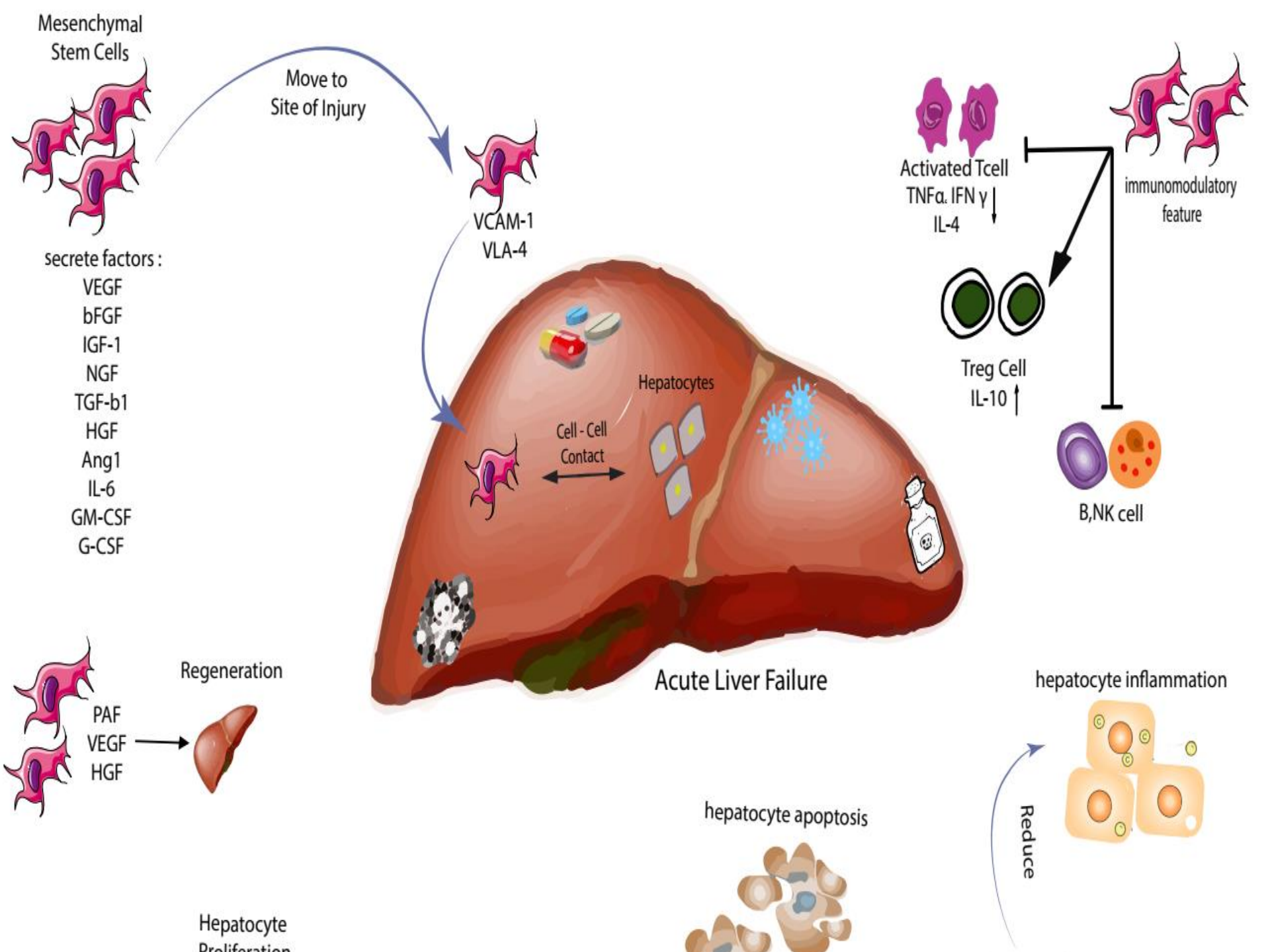
- Vascular endothelial growth factor (VEGF)
- Insulin-like growth factor 1 (IGF-1)
- basic fibroblast growth factor (bFGF),
- Nerve growth factor (NGF)
- Transforming growth factor beta-1 (TGF-b1)
- Placental growth factor (PGF)
- Stromal cell-derived factor 1 (SDF-1/CXCL12)
- Monocyte chemoattractant protein-1 (MCP 1/CCL2)
- Hepatocyte growth factor (HGF), interleukin-6 (IL-6), IL-8, IL-10, IL-13,G-CSF and GM-CSF.

Placenta-derived mesenchymal stem cells

- The placenta is one of the largest organs with an essential role in the development of the fetus, which plays a role in the secretion of nutrients for the fetus and immune protection (tolerance) of it.

- PD-MSCs possess self-renewal capacity
- Have multilineage differentiation
- Lack ethical problems
- Accessible
- Abundant
- Show strong immunosuppressive effects

Heo JS, Comparison of molecular profiles of human mesenchymal stem cells derived from bone marrow, umbilical cord blood, placenta and adipose tissue, 2016.


Mesenchymal Stem Cells
Move to Site of Injury
VCAM-1
VLA-4
secrete factors :
VEGF
bFGF
IGF-1
NGF
TGF-b1
HGF
Ang1
IL-6
GM-CSF
G-CSF
Activated Tcell
TNFα, IFN γ
IL-4
immunomodulatory feature
Treg Cell
IL-10
B,NK cell
Hepatocytes
Cell - Cell Contact
Acute Liver Failure
PAF
VEGF
HGF
Regeneration
hepatocyte inflammation
Reduce
hepatocyte apoptosis
Hepatocyte

Clinical trials of MSCs

- The first clinical trials of MSCs were completed in 1995 when a group of 15 patients were injected with cultured MSCs to test the safety of the treatment.

- Since then, more than 200 clinical trials have been started. However, most are still in the safety stage of testing.

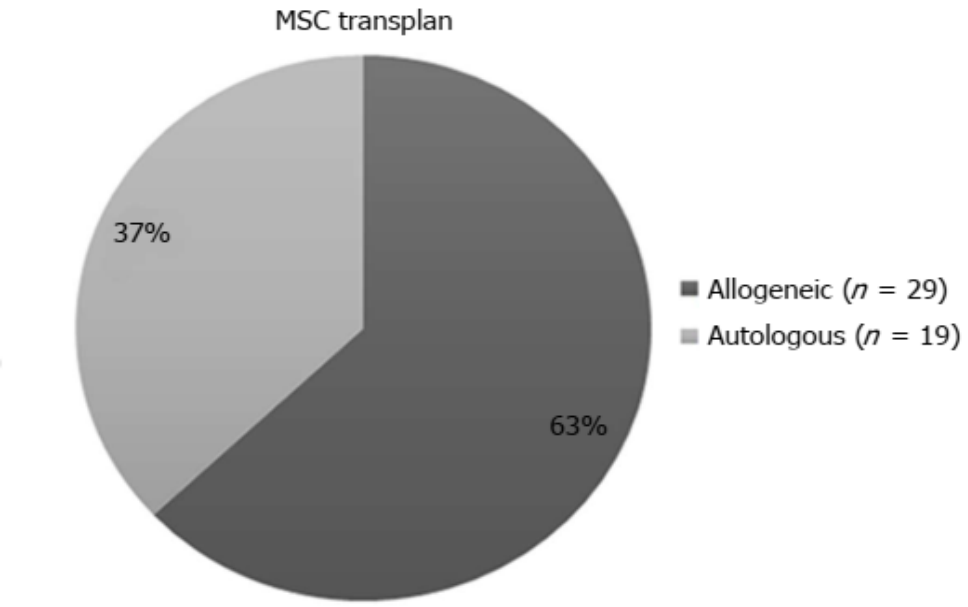
Wang S, Qu X, Zhao RC (April 2012). "Clinical applications of mesenchymal stem cells". *Journal of Hematology & Oncology*. **5**: 19. doi:10.1186/1756-8722-5-19

- Embryonic stem cells are isolated from embryonic tissues, especially multiple extraembryonic tissues.

- Tissues such as amniotic fluid, Wharton's jelly, amnion, chorion,embryonic membrane and placenta have MSCs.

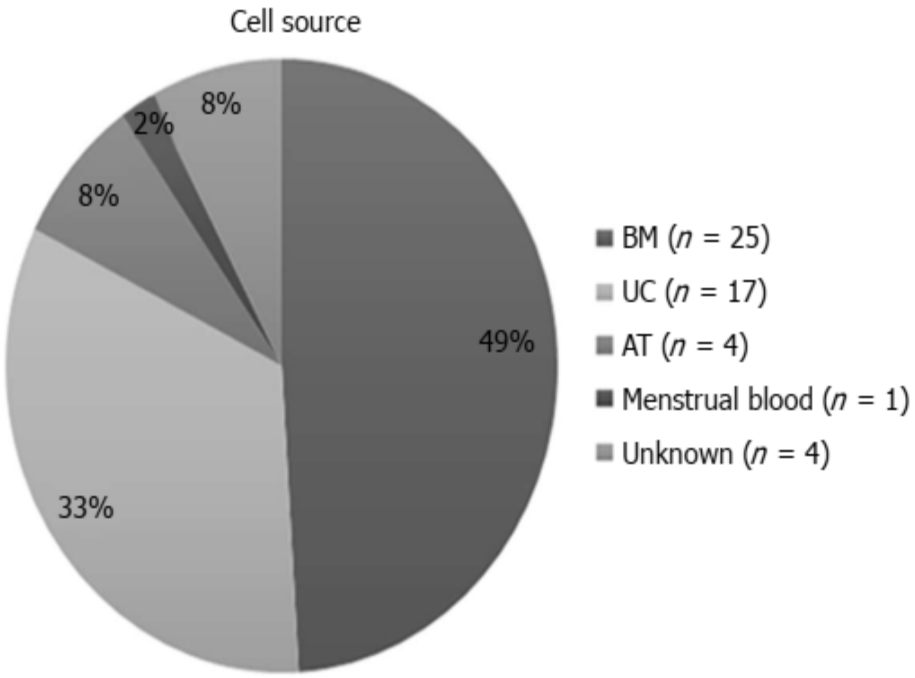
- The placenta is one of the largest organs with an essential role in the development of the fetus, which plays a role in the secretion of nutrients for the fetus and immune protection (tolerance) of it. It has recently been observed that PD-MSC are a new alternative source of MSCs for regenerative therapies [78].

Clinical trials in liver disease using mesenchymal stem cells



Fiore EJ et al. Mesenchymal stromal cells and extracellular vesicles in liver regeneration

Clinical trials in liver disease using mesenchymal stem cells



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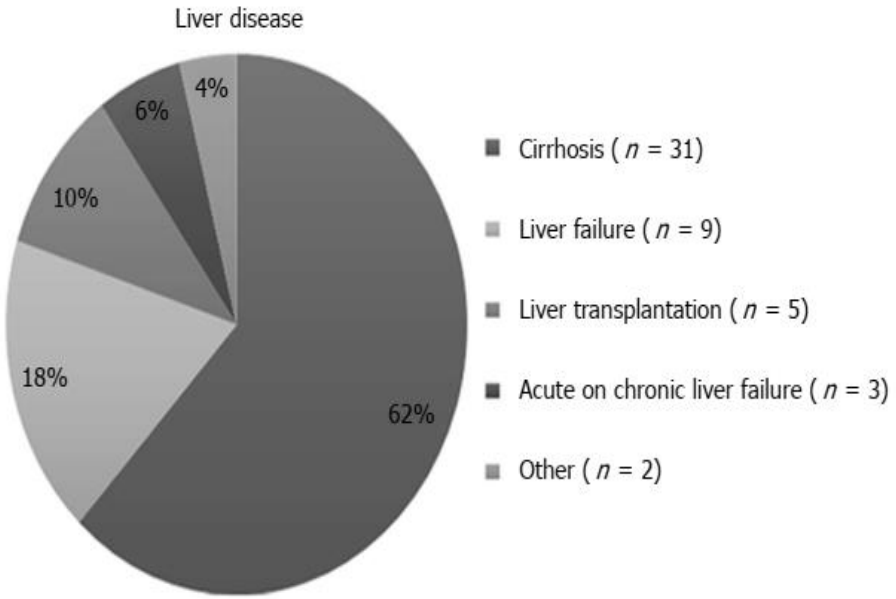

Fiore EJ et al. Mesenchymal stromal cells and extracellular vesicles in liver regeneration

Placenta-derived mesenchymal stem cells

PD-MSCs can be considered as a good allogeneic source for ALF in future because of their safety, easy accessibility, lack of immune system stimulation, secretion of appropriate factors for liver tissue and healing properties.

نتایج	مدل حیوانی	نحوه تزریق	دوز سلول بنیادی مزانشیمی	منبع سلول بنیادی مزانشیمی	نویسنده اول/سال
accelerate liver regeneration of ALF through PDGF and VEGF regulation	ALF/ Rat	tail vein	1 x 106	UC-MSCs	Agung Putra 2018
hUC-MSCs can rescue ALF and repopulate the livers of rats through the stimulation of endogenous liver regeneration & inhibition of hepatocellular apoptosis	ALF/ Rat	tail vein	1 × 107 cells/ kg	hUC-MSCs	Yongting Zhang ۲۰۱۸
prevented death & irreversible liver injury	ALF/ Rat	portal vein	1*106	hepatocyte-like Cells WJ-MSCs	Shih-Yi Kao ۲۰۱۵
liver regeneration via proliferation and transdifferentiation into hepatocytes during the initial stage of FHF	FHF/ Pig	intraportal peripheral vein	3 * 107	hBMSC	Jun Li ۲۰۱۲
differentiate into hepatocyte-like cells in vitro and in Vivo prolong the survival time of ALF pigs	ALF/ Pig	jugular vein / Portal vein	1.0 × 108	hPMSCs	Hongcui Cao 2012

نویسنده اول/سال	منبع سلول بنیادی مزانشیمی	دوز سلول بنیادی مزانشیمی	نحوه تزریق	بیماری	نتایج
Liang Peng ۲۰۱۱	Auto-BM MSCs	-	hepatic artery	patients with chronic hepatitis B–induced liver failure (ACLF)	ALB, TBIL, and PT and MELD score Improved Short-term efficacy was favorable,
MING SHI 2012	UC-MSC	0.5 * 106 Cells/kg	IV three times at 4-week intervals	Acute-on-chronic liver failure (ACLF)	increased the survival rates Reduced MELD Score increased serum albumin, cholinesterase, and prothrombin activity; and increased platelet counts
Yu-Hua Li ۲۰۱۶	UC-MSC plasma exchange (PE)	100 × 106 cells	infusion pump into the liver single transplantation	HBV-ACLF	MELD Score , Levels of albumin, PT and INR were markedly improved
Wen-xiong Xu 2018	UC-MSCs combined with PE treatment	105 cells/kg	IV once a week, 4 times	HBV-ACLF	levels of total bilirubin, alanine aminotransferase, aspartate transaminase, and MELD score were significantly decreased

نتایج	بیماری	نحوه تزریق	دوز سلول بنیادی مزانشیمی	منبع سلول بنیادی مزانشیمی	نویسنده اول/سال
MELD score Serum albumin, INR, T Bil improved Infusion of CD34+ stem cells through the hepatic artery is not safe in decompensated cirrhosis	decompensated cirrhosis	hepatic artery	3 to 10 million CD34+ cells	HSCs	Mehdi Mohamadnejad 2007
Decreased MELD in 2 of 4 patients the quality of life Improved	decompensated liver cirrhosis	peripheral vein	mean 31.73×106	Auto-BM MSCs	Mehdi Mohamadnejad 2007
no signicant alterations of liver function parameters, liver enzymes, serum albumin, creatinine, serum bilirubin and/or liver volume after transplantation of both types of autologous cells in these patients	Decompensated liver cirrhosis	Portal vein	BMSCs 1.31±0.14 ×109 BM-derived CD133+ 6.4±3.2 ×106	BMSCs BM-derived CD133+	Saman Nikeghbalian 2010
No differences between the groups	decompensated liver cirrhosis	Single dose, peripheral vein	Median of 1.95 × 108 (range: 1.2-2.95)	BM-MSC	Mohamadnejad 2013
Lung Liver Spleen	Tracking in cirrhosis	IV	250–400×106 cells	111In-oxine labeled mesenchymal stem cells	Ali Gholamrezanezhad 2011

Thank You