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Review Article

Injury Mechanism in Liver Transplantation and its Protective Measures

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Submitted: 04 May 2016

Accepted: 05 July 2016

Published: 08 July 2016

ISSN: 2333-7117

Keywords

- Injury before liver procurement
- Cold preservation injury
- Ischemia-reperfusion injury
- Pretreatment
- Mechanical perfusion

Abstract

This paper will explore mainly donated by brain dead liver donors (DBD). Brain death could induce much physiological and metabolic change in tissues, which is associated with hemodynamic instability and the increase of inflammatory mediators. Injury of donor liver mainly includes the injury before liver procurement, cold preservation injury, and ischemia-reperfusion injury. Liver preservation, immunosuppressant, and transplant operation are three key technologies for liver transplantation. Benefited from the development and application of new immunosuppressants and modern surgical techniques in the past 20 years, great progress in liver transplantation has been achieved in China. The purpose of this paper is to summarize the research progress in liver transplantation including the mechanism of liver injury in transplantation and its protective measurements.

INTRODUCTION

After the first human liver transplant (LT) was performed in America, Colorado in 1963 by Starzl, LT has become the only safe curative treatment for the end-stage liver diseases with almost 50 years of development[1]. Nevertheless, there is still a lot of factors restrict the clinical effect of liver transplantation, such as primary non-function (PNF), the prevention of recurrence of original disease, transplantation immune tolerance, chronic graft dysfunction, cold preservation, ischemic reperfusion injury, postoperative complications, and liver source shortage [2-5]. The prerequisite for successful organ transplantation is the high donor quality, so how to keep donor quality and function in a good status is particularly important. The following of this paper is to describe the mechanism of liver injury in transplantation[6,7], which may lead to early graft dysfunction, and protective methods in liver transplantation.

Injury mechanism in liver transplantation

In the developed countries, organ donation of transplantation donors after citizen's death (DCD), including liver donors collected from the brain death (DBD), cardiac death (DCD) and brain heart double death (DBCD), this paper will explore mainly donated by brain dead liver donors. The injury of donor liver mainly includes the injury before liver procurement, cold preservation injury, and ischemia-reperfusion injury.

Injury before liver procurement

The injury before liver preservation refers to the existing injury or damage before perfusion of cold preservation solution [8-11], the main factors including: the liver lesion, donor age, blood biochemistry, damages related with brain death or caused by brain death and marginal donor organs. On the other hand, fatty degeneration of the liver is a common hepatic disease, which is easy to cause higher primary non function (PNF). Among donor organs, liver is the high application of organs due to its high tolerance to ischemia, hypoxia and regeneration ability. Donor safety has been of prime concern in the liver transplantation, so maintaining good characteristic and correcting all kinds of internal environment disorder are important protective measures for donor liver.

Cold preservation injury

Even if cold preservation has adverse effects on the liver, it is still one of the most important measures for donor liver preservation. Low temperature can reduce the oxygen consumption, decreased liver metabolism, beneficial to ATP storage, and improve the tolerance of ischemia. But it also has adverse effect of low temperature classical effect during the cold preservation [12-16] (1) low temperature can cause loss of energy

and substrate at non-physiological state, (2) anaerobic glycolysis leads to accumulation of lactic acid, so the low temperature could cause intracellular acidosis, (3) cold preservation would produce active substances with oxygen free radical scan, resulting in organ damage, (4) low temperature can inhibit Na^+-K^+-ATP enzyme on liver cell membrane, which promote the accumulation of intracellular Na^+ and destroy ion balance, leading to intracellular edema [17,18], (5) low temperature will damage the enzyme, cell membrane potential, and the function of transportation, leading to the breakdown of protein structure, (6) the amount of oxygen release will be reduced at low temperature due to the variation of oxygen dissociation curve, resulting in tissue hypoxia.

Ischemia-reperfusion injury

For the ideal receptors, graft perfusion blood is normal containing unactivated white blood cells and platelets, meanwhile the oxygen and the level of inflammatory mediators are normal, ischemia-reperfusion injury should be nonexistence. In fact, ischemia-reperfusion injury is inevitable during liver transplantation, much physiological and metabolic changes in tissues, and complete organ destruction may also occur. Hepatic ischemia reperfusion injury is a continuous process of damage of liver cells, and the extent of the damage depends on the following three aspects: (a) the degree of white blood cell and platelet direct to adhere endothelial cells and been activated; (b) the extent of activation of Kupffer cells, (c) inflammatory mediators and oxygen produced from the cells and other sources. In the reperfusion period, the change of various components in the blood could cause organ damage [19-21].

Platelet: The activation of endothelial cell wall leads to the adhesion and activation of platelet [22,23], whose mechanism can be attributed to the increasing of the expression of hepatic sinusoidal cells [15,24]. Nitric oxide produced by platelet, and oxygen free radicals generated in ischemic liver re-oxygenation can cause the generation of peroxynitrite, while the latter is a kind of endothelial cell apoptosis inducer with very high activity.

White blood cells: Leukocyte adheres to hepatic sinus rapidly after reperfusion, resulting in significant damage to the liver [25-29]. The Kupffer cells are activated at the moment the reperfusion is start-up. Activated Kupffer cells could release tumor necrosis factor-alpha (TNF-a) and interleukin 1 (IL-1), inducing the increase of expression of leukocyte CD11b and improvement of the recruitment of these cells to the liver blood sinus. Kupffer cells play an important role in the mechanism of injury mediated by the endothelial cells [30].

Endothelial cell apoptosis or necrosis: Recently, studies have shown that the death of sinusoidal endothelial cells (SEC) through apoptosis [31,32]. The number of apoptotic cells goes together with graft activity. Therefore, apoptosis should be the main mechanism in ischemia-reperfusion injury. In addition, the preservation liquid containing anti-apoptotic drugs has a protective effect on donor organs, indicating that apoptosis is very important in liver preservation and reperfusion injury [33,34].

Reactive oxygen species: There is plenty of evidences show that reactive oxygen species (ROS) could exert an important influence on reperfusion injury, while Kupffer cells are the major source of ROS. Ischemia can activate Kupffer cells, which become the most important source of vascular ROS in reperfusion period [35,36].

Protease: Calpain, caspase, and other cysteine proteinases, which act as medium for preservation-reperfusion injury, can regulate cell apoptosis and necrosis [37,38]. Calpain is a calcium dependent non-lysosomal cysteine protease which related to hydrolysis of protein in cytoskeleton and cell membrane. The activity of calpain increased significantly during cold ischemia, which will further increase after reperfusion [39].

Protective methods in liver preservation

The following describes the new protective strategies in improving liver preservation.

Pretreatment: Ischemic preconditioning is a new protective measure for protect liver from ischemia-reperfusion injury, that is, organ endures a period of transient ischemia and reperfusion before long time ischemic stress [40]. Pretreatment can effectively prevent the liver from ischemia-reperfusion injury under normal temperature, which can turn the liver damage which might cause animal death into a non-fatal injury. The ischemia preconditioning before reperfusion is effective, which can play an important role in the whole ischemia-reperfusion period [41].

Machine perfusion: *In vitro* mechanical perfusion system as a pathway of blocking the biodegradation has good effect for preservation of organization [42-44]. Machine perfusion continuously provides necessary materials (such as glucose, amino acids, nucleotides, oxygen) for transplantation, and conducts timely treatment of metabolite to maintain the vitality of the organ. Oxygen is the power source of all cell activities to support the generation of ATP from cells. In ischemia preservation, organ blood stops to flow and provide oxygen and nutrients. The reduction of the loss of ATP is the key to control the ischemic injury cascade effect, which need to use oxygenated solution for liver perfusion [45].

Pretreatment and machine perfusion have been usually applied to reduce the injury in liver transplantation, and these methods combined with drugs could have great prospect for decrease injury [46-49].

CONCLUSION

The research progress of the mechanism of LT is described in detail in this paper. The injury of donor liver mainly includes the injury before liver procurement, cold preservation injury and ischemia-reperfusion injury. Liver ischemia reperfusion injury is a kind of antigen non-dependent acquired injury, which is an important problem in transplantation. In sum, the reasonable choice of donor, reduce the warm, cold ischemia time, and multiple levels of intervention based on the molecular level of liver transplantation and reperfusion injury, is expected to effectively improve the prognosis of liver transplantation patients.

ACKNOWLEDGEMENTS

This report was financially supported by National Natural Science Foundation of China-Xinjiang joint fund (U1403222).

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Cite this article

Peng N, Ai Z, Wang Y, Ye Q (2016) Injury Mechanism in Liver Transplantation and its Protective Measures. JSM Biotechnol Bioeng 3(2): 1054.