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Bioengineering in Organ Transplantation: Targeting the Liver

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Abstract

About 27,000 deaths are registered annually in the United States due to liver disease. At this time, the only definitive treatment of hepatic failure is orthotopic transplantation. However, there is a critical shortage of organs with the total waiting list for all organs currently at 100,000 requests. The number is increasing by 5% every year. Given that only organs in pristine condition are transplantable and that the hidden demand for organs as an anti-aging solution will be many times the current figures, orthotopic transplantation will always remain a limited pool. The increasing donor organ shortage requires consideration of alternative emerging technologies. Regenerative medicine may offer novel strategies to treat patients with end-stage organ failure. The ultimate aim of cell transplantation, tissue engineering, and stem cells is to regenerate tissues and organs. With the development of whole organ decellularization methods, the equation of organ shortage may dramatically change in the near future. Decellularized organs provide the ideal transplantable scaffold with all the necessary microstructure and extracellular cues for cell attachment, differentiation, vascularization, and function. New techniques to re-engineer organs may have major implications for the fields of drug discovery, regeneration biology, and ultimately organ transplantation. In this review we have provided an overview of complementary approaches to study and enhance the success of organ repopulation strategies creating new grafts/organs for transplantation.

The Donor liver shortage for orthotopic transplantation is considered to be about 27,000 deaths registered annually in the United States due to these diseases.[1] To date the only definitive treatment for hepatic failure is orthotopic transplantation. About 10,000 patients are added to the waiting list each year. Less than 7000 individuals receive transplantations each year (http://www.optn.org/). It is estimated that in the next decade the high prevalence of hepatitis C (~3%) will increase the demand significantly.[2] The donor pool, in contrast, is expected to shrink due to the obesity epidemic because steatosis being common in donors is a significant risk factor for liver transplantation.[3] Moreover, about 10,000 patients undergo hepatic resection every year to treat malignancies. Many of them experience liver functional impairment due to the reduced absolute amount of hepatic parenchyma.[4] Therefore, the need for practical therapies for liver failure is extremely urgent.

The solutions being considered to resolve the donor shortage can be classified into 2 categories. The first category includes efforts to make more organs available, as by xeno-

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transplantation, which could provide a limitless supply of donor organs. However, previous attempts in humans often resulted in hyperacute rejection and death.[5] The second category is marginal donor organ resuscitation with machine perfusion. These studies are a promising alternative, but these organs show significantly shorter survival. The machine perfusion presents a variety of practical and logistical issues.[6] In any case, the total number of organs that can be reconditioned is estimated to be about 6000,[7] which is well below the current death rate of 27,000 per year.

Since in many cases of acute failure and hepatic resection the liver shows an ability to regenerate temporary, limited hepatic support may obviate the need for transplantation, which would free up donor livers. In addition, avoiding transplantation eliminates the need for life-long immunosuppression, thereby translating into significant costsavings for the healthcare system. One such alternative is Extracorporeal Bioartifical Livers (BALs) containing functioning viable hepatocytes, which could provide temporary support for patients with fulminant hepatic failure or awaiting orthotopic liver transplantation. However, after 3 decades of research, clinical success has yet to be achieved.[8]

A much more elegant solution to liver disease is hepatocyte transplantation. Laboratory studies and experiences in small numbers of human subjects have demonstrated its efficacy.[9] Cell transplantation is a practical procedure compared with organ transplantation. It can be performed with much less risk to the patient, and much reduced cost to the healthcare system. Furthermore, because it is not as invasive, it can also be applied to patients who are severely ill and would not be able to tolerate organ transplantation. Unfortunately, cell transplantation therapy is also limited by the severe shortage of donor cells as well as by low transplant efficiency. Nevertheless, new strategies to enhance cell engraftment and repopulation suggest the benefits of radiation therapy with potential clinical translation in the near future. However, suitable preclinical models have not yet been produced.[10]

There is an increasingly large body of literature indicating that tissue-specific gene expression, morphogenesis, and cell migration are promoted by interactions between cells and their surrounding extracellular matrix (ECM); the liver is not an exception.[11] Recently, interest in decellularization techniques has increased significantly, wherein removal of the cells from an organ leaves a complex mixture of structural and functional proteins that constitute the ECM.[12]

This procedure has been applied in a variety of organs including the liver.[13–17] It is rational to expect that biological scaffolds derived from decellularized livers would provide an adequate distribution of ECM proteins for cell differentiation, hence preventing the hepatic dedifferentiation commonly observed in hepatocyte cultures using plastic-surface monolayers. The scaffold structure is also likely to provide the necessary architecture for cell engraftment. Moreover, the scaffold contains a perfusable vascular tree that facilitates reconnection to the blood torrent, which can greatly enhance cell survival upon transplantation. The number of available discarded livers for recellularization is estimated to be about in the order of 100 or about 40% of the eligible deaths in the United States.[18] Therefore, the concept of engineering liver grafts from discarded organ ECM is feasible without affecting the number of organs that actually are reserved for transplantation. Therefore, the native liver matrix may represent the ideal structure-scaffold for cell engraftment, differentiation, and cell transplantation.

In conclusion, cell transplantation is an elegant approach to treat or prevent liver failure. It could save tens of thousands of lives each year. However, 2 key obstacles prevent it from reaching widespread clinical use: the lack of transplantable cells, and their poor engraftment leading to insufficient long-term functionality and viability. The evidence reviewed herein

supports the conclusion that realization of cell transplantation methods might be enhanced with new strategies to enhance the engraftment of liver cells providing them with a growth advantage, namely, new bioengineering technologies of an ideal transplantable scaffold with the necessary microstructure and extracellular cues for cell attachment, differentiation, vascularization, and function after repopulation with hepatocytes derived from stem cells. An exciting possibility from recent developments is to use the decellularized liver ECM as a scaffold for cell transplantation, ultimately allowing the development of engineered auxiliary liver grafts for transplantation.

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