



Stem-cell-activated organ following ultrasound exposure: Better transplant option for organ transplantation

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SUMMARY

Although doctors try their best to protect transplants during surgery, there remain great challenges for the higher survival rate and less rejection of transplants after organ transplantation. Growing evidence indicates that the stem cells could function after injury rather than aging, implying that suitable injury may activate the stem cells of damaged organs. Furthermore, it has been revealed that stem cells can be used to induce tolerance in transplantation and the ultrasound has great biological effects on organs. Basing on these facts, we hypothesize that the stem cells within the transplants can be activated by ultrasound with high-frequency and medium-intensity. Therefore, the stem-cell-activated organs (SCAO) can be derived, and the SCAO will be better transplant option for organ transplantation. We postulate the ultrasound can change the molecular activity and/or quantity of the stem cells, the membrane permeability, the cell-cell junctions, and their surrounding microenvironments. As a result, the stem cells are activated, and the SCAO will acquire more regenerative capacity and less rejection. In the paper, we also discuss the process, methods and models for verifying the theory, and the consequences. We believe the theory may provide a practical method for the clinical application of the ultrasound and stem cells in organ transplantation.

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Introduction

Despite of effectiveness on patients with end-stage organ diseases, organ transplantation is greatly restricted by the survival rate and graft-rejection. Recently, researchers begin to pin their hope on stem cell transplantation. However, it seems impossible for the ideal treatment to be applied in clinical within a short time, as it is unclear whether the transplantation of cultured stem cells will cause unlimited proliferative disease, such as tumor, etc. Moreover, it is still perplexing how to accurately induce the differentiation of stem cells to form organs or tissues we need.

Growing evidences revealed the stem cells could function after injury rather than aging, implying that injury may activate the stem cells of damaged organs. It has been discovered the stem cells refreshed adult mammalian cardiomyocytes after injury while they did not function on uninjured cardiomyocytes [1]. Another study reported that stem cells in the hair follicle bulge contributed to wound repair but not to homeostasis of the epidermis [2]. Furthermore, stem cells can be used to induce tolerance in transplantation. It has been revealed that, after transplantation of combined kidney

or liver and hematopoietic stem cells, patients lived for several years without any rejection [3–5]. Some scholars conjectured that the mesenchymal stem cells might be used to induce tolerance in heart transplantation [6–8]. Therefore, it is likely that the activation of stem cells within organs may help obtain better transplants. We believe doctors will have a preference to suitably injure organs in situ to obtain the stem-cell-activated transplants before surgery, rather than traditionally try their utmost to protect the organs from any additional wound.

The hypothesis

The hypothesis

The stem cells can function following organ injury rather than aging, and induce tolerance after allograft, indicating that the damaged organs with activated stem cells may be more powerful than those whole ones for organ transplantation. Thus, we hypothesize that the stem cells within the donor's organ can be activated by ultrasound with high-frequency and medium-intensity, therefore, the stem-cell-activated organs (SCAO) can be derived. We believe the SCAO is better transplant option for organ transplantation, and the application of SCAO may help achieve much more satisfactory result.

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As stem cells keep static by regulation of normal microenvironments [9–11], we postulate that suitable ultrasound injury of the organ can change the molecule activity of the stem cells, the membrane permeability, the cell–cell junctions, and their surrounding microenvironments. Thus, the stem cells are activated and the SCAO can be obtained. Besides their potential in regenerative medicine, these low differentiated cells may also have great immunoregulatory capacity. To escape immune response and induce tolerance, they may choose to alter the cytokine secretion profile to induce a shift toward the tolerant phenotype, rather than activate the T cells [7,8]. As a result, the stem cells become compatible with both two microenvironments and form compatible organ of new hybrid immune system. Consequently, the transplants are remodeled or replaced by cells of great regenerative and tolerant functions, and it will be easier for the SCAO to survive with less rejection.

Why ultrasound is selected and how does it activate stem cells?

Ultrasound has been widely used in many medical fields, including but not limited to diagnostic imaging and ultrasonic therapy. The reason why ultrasound is chosen is that, compared with other manipulations, such as scalpel, laser, etc., the ultrasound is a better choice in security, controllability and precision. Studies have suggested that ultrasound with frequency, intensity and duration fully in the diagnostic range have significant biological effects [12,13]. Unsworth et al. [14] observed dramatic increase in alkaline phosphatase and MMP-13 mRNA levels examined in ultrasound-treated cultures compared with untreated controls when they cultured the preosteoblast cells. Bertuglia et al. [15] demonstrated ultrasound exposure increased endothelial permeability, which is an early and reversible sign of morphologic change of the membrane. They presumed that the reason was likely owing to loosening of cell-to-cell tight junctions for mechanical low-amplitude vibration and the low-level endothelial damage might lead to a state of increased resistance during reperfusion. Other researchers believed that therapeutic ultrasound can be used for dental tissue regeneration [16].

Accordingly, we postulate that focused ultrasound with suitable frequency and intensity could activate the stem cells through concentrating those biological effects on the niche. Focusing on the niche rather than the surround tissues, ultrasound will exhibit a great influence. The niche may turn to be an ‘activated’ house full of activated stem cells. For the stem cells, the molecular quantity and/or activity, the membrane permeability and the cell–cell junctions will be changed, implying that they cannot keep normal contact with each other and their surrounding environments. In response, they begin functioning to proliferate, migrate and repair damage. Consequently, they are activated and the SCAO forms.

Why does the SCAO become better transplant?

There are three points having to be addressed for this problem. First, the ultrasound injury properly concusses the niche microenvironment where the stem cell populations reside and keep static, which aims to activate the stem cells. Meanwhile, it would not change the original architecture of organs, which is maximally in favor of the rapid recovery and growth of the transplants within the recipients. The ultrasound damage of transplants may cause a state of increased resistance during reperfusion [12]. Second, compared with the whole organ, the SCAO will have more powerful capacity of survival and regeneration, and induce better tolerance because of the existence of activated stem cells. Third, in contrast with the stem cells cultured in vitro, the SCAO are safer for patients by reason that the stem cells are not forced to depart from their original microenvironment.

As a result, the application of SCAO for transplantation may lead to the achievement of higher survival rate and less graft-rejection in the clinic. Although it is still necessary for patients to take immunosuppressant within a few months, we believe reduction of those drugs can be achieved. With depth research on the immune tolerance of stem cells, the problem will be finally solved. Furthermore, to verify the hypothesis, we divide the SCAO into whole SCAO and part SCAO. At least two of the part SCAO could be harvested from one organ, which may help relieve the stress of organ shortage.

Why are not the stem cells activated during normal transplantation?

It is generally believed that organ transplantation is great damage to both the donor and recipient, why do not the stem cells function? During traditional organ transplantation, doctors try their best to protect the integrity and non-invasive of organs rather than destroy them. For example, after blocking the blood supply, they begin to remove the whole liver and transfer it to the recipient who is suffering vascular ligation. In the process, the liver itself does not receive enough injury to invoke stem cells. Even if there is transient activation of stem cells, they may rapidly differentiate to normal cells rather than invoke more companions as those insignificant wound cannot lead to significant change of the niche.

Verification and consequences of the hypothesis

Verification process

The main process for authenticating the theory includes location of the niche, ultrasonic irradiation, and organ transplantation. First, precise positioning of the niche is necessary for doctors to operate on. For example, the canals of Hering contain the facultative hepatic stem cells in humans [17]. Second, the ultrasound with suitable frequency and intensity will be used to function on the niche, during which duration time can be explored. Third, following exposure of ultrasound, the injured organ can be transplanted normally to the recipients. In addition, animal experiments on rats or mice are needed to be done before clinical application of the theory. Through these studies the ultrasound with exact frequency, intensity and duration will be clearly explored.

Verification methods and consequences

What is the suitable ultrasound that can help verify the hypothesis?

In order to verify the hypothesis, suitable ultrasound injury is very important for activation of stem cells of the transplants. Currently, high-frequency (2–40 MHz) and low intensity ultrasound is used for diagnostic imaging, as it can show clear and detailed imaging with less tissue injury. In contrast, low-frequency (<1 MHz) and high intensity ultrasound is applicable to ultrasound therapy. For example, high intensity focused ultrasound can be used to remove tumor tissue. The above-motivated facts indicate that there must be suitable frequency and intensity range for ultrasound to accurately wound the niche. Therefore, we believe the ultrasound with high-frequency and medium-intensity is ideal to activate stem cells. High-frequency guarantees image quality, while medium-intensity avoids excessive trauma and leads to suitable niche injury. Through stimulating the niche narrowly, the high-frequency and medium-intensity ultrasound can make a great change in molecular quantity and activity, membrane permeability, cell–cell junctions and signal communications between the niche and their surrounding environments. As a result, the stem cells can be activated.

Categories of the SCAO

As mentioned above, the high-frequency and medium-intensity ultrasound can damage niche, activate stem cells and form SCAO. Further, the SCAO can be divided into two kinds of organs: whole SCAO and part SCAO. The former can be defined as whole organ of damaged niche and the latter part of the organ with the damaged niche. So the whole SCAO can be derived as long as we damage the niche areas of transplanted organs. Then, the stem cells are activated and reform a hybrid organ, which may be more compatible with the recipient. On the other hand, for some organs of powerfully compensatory and regenerative capacity, the part SCAO can be obtained if the whole SCAO is cut off along the centric axis before the ultrasound manipulation. Thus, one organ can be transplanted into two recipients, which may help ease the problem of donor shortage.

Models for authenticating the hypothesis

To test the theory, appropriate models are necessary. The liver and hair follicle are excellent clinical models to demonstrate the hypothesis. Specifically, the liver can be employed to help put both the whole and part SCAO into practice because of the strong regeneration capacity. It has been revealed that the hepatic stem cell niche could form in liver injury [18], suggesting feasibility of the part SCAO for more effective transplantation. Also, the hair follicle is a mini-organ as well as an available model for organ transplantation due to the large number and easy non-invasive acquisition. Most importantly, the niche of the hair follicle has been located in the bulge [19], which lays a solid foundation for verifying the hypothesis.

Conclusion

In summary, we put forward that the stem-cell-activated organ can be used for organ transplantation and may achieve satisfactory effect. The hypothesis will provide a simple and safe method for the application of ultrasound and stem cells for patients needing organ transplantation.

Conflicts of interest statement

None declared.

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