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Development of bio-artificial micro-vessels with immunosuppressive capacities: a hope for future transplantations and organoids

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Background: From creating artificial organs to transplantation and cancer, newly formed vessels are playing a critical role. Endothelial progenitor cells (EPCs) are non-differentiated endothelial cells which are present in circulation and are applied in neovascularization and correction of damaged endothelial sites. In culture, EPCs generate endothelial colony forming cells (ECFCs) that have endothelial features but still retain properties of stem/progenitor cells. However, these cells which are recognized as CD31⁺CD144⁺KDR⁺ are very rare in blood stream. Therefore, it is necessary to be ex-vivo expanded for further applications. Since EPCs from patients are proved to be impaired and inefficient, allogenic sources either from adult or cord blood are considered as good alternatives. Due to the reaction of immune response to allogenic cells which usually leads to increased immune response and inflammation and finally elimination of injected cells, we have focused on the exact role of EPCs on immune cells, particularly, T cells which are the most important cells applied in immune rejection.

Aims: First we sought to design and produce a biomimetic micro-vessel device and to endothelialize it in static and under flow conditions. Second, we wanted to investigate the interaction between EPCs and T cells to further understand their potential immunogenicity.

Results: For the first part of the study we have been able to produce a biomimetic micro-vessel device that is porous, biocompatible, soft and transparent for high-resolution microscopy techniques. We have developed a multi-scale microfluidic chips with a conventional design of successive branching for fluid injection into the capillaries following Murray's laws (Figure 1A). Furthermore, we have successfully endothelialized this artificial micro-vessel using cord blood derived EPCs both in static and under flow condition and kept them in an acceptable situation up to 2 weeks after the first seeding (Figure 1B and C).

For the second part of our study, we have shown for the first time that in contrary to already differentiated endothelial cells, EPCs while co-cultured with T cells, not only do not increase T cell proliferation but also are extremely immunosuppressant (Figure 1D). Moreover, we have shown that EPCs could also reduce the activation markers expressed by both CD4⁺ and CD8⁺ conventional T cells.

Conclusion: We have demonstrated for the first time the possibility of producing an endothelialized vessel-like micro chamber with remarkable immunosuppressive and immunomodulatory properties. This proves the importance of using EPCs for future bio-artificial organs since these cells not only do not increase allo-response but also can regulate it. In case of transplantation, our findings could open a door for ameliorating the transplant acceptance through faster endothelialization and suppression of alloreactive T cells aiming to reject the transplant.

Key words: bio-artificial micro-vessels, Endothelial progenitor cells, Immunosuppression

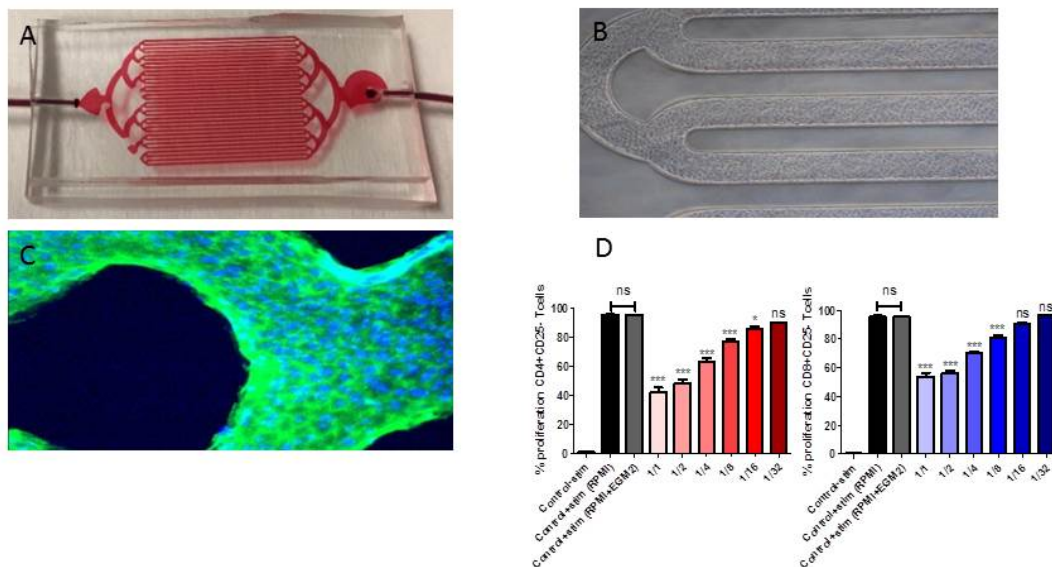


Figure 1: Representation of biomimetic micro-vessel device under flow. A) This device is consist of 32 channels of 300 μm width and 35 μm height. B) This image depicts a successful endothelialization of biomimetic micro-vessel device. C) Immune staining of endothelial progenitor cells under flow condition showing a complete endothelialization of the device. Green color represents CD31 marker and Blue color represents DAPI marker. D) EPCs derived from cord blood are remarkably immunosuppressant for both CD4+ and CD8+ responder T cells in a dose dependent manner. Data are represented as mean \pm SEM. ns, nonsignificant. *P < .05; **P < .01; ***P < .001