Advanced culture systems for *ex vivo* human vascular tissue conditioning

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Abstract

Our experience shows that using bioengineering approaches facilitates the understanding of vascular physio-pathological mechanisms and, in perspective, will speed up the development of new life-saving treatments. The use of human samples, particularly operating room-derived samples, which would have been otherwise discarded, is a very valuable approach. In line with the 3Rs principles, this methodology is worth the cost of being set up and managed, wherever and whenever possible.

Introduction

The conventional methods used to study vascular diseases at a supra-cellular level mainly involve animal models. On the other hand, in line with the 3Rs spirit, we developed several *ex vivo* culture systems, specifically designed to host human vascular tissue samples obtained as discarded pieces from the operating room (OR). We conceived simple and easy-to-use culture chambers, with a common distinctive feature, that is comprising some *ad-hoc*-developed chassis integrated into conventional-like lab equipment. Such culture chambers are meant for hosting native or engineered vessels, coupled with control and fluidic systems, enabling realistic and dynamic culture conditions. This approach allows investigating human tissue maladaptation in a tightly controlled environment.

Materials and Methods

Cyclic pressure culture system

This culture system model is designed to apply a feedback-controlled cyclic pressure stimulus (*e.g.*, 80-120 mmHg), within a controlled environment. We used this system to investigate the effects of strain wall mechanical stimulus on native vessels such as human saphenous veins (hSV).[1,2] We also used the system to study and promote possible enhancements in the maturation of engineered constructs.[3,4]

Coronary-hemodynamics system

A compact, modular, and low-priming-volume pulsatile simulator was designed enabling stimulating hSVs under realistic coronary artery bypass graft (CABG) conditions and venous perfusion (VP) conditions, involving the control of both the pressure pattern and the flowrate pattern (CABG: P = 80-120 mmHg, Q_{mean} = 150-170 mL/min; VP: P = 5 mmHg; Q_{mean} = 3 mL/min).

Double-compartment culture systems

These systems have been designed to replicate differential conditions in the luminal and adventitial environments. We developed two different culture chambers: i) a falcon-tube layout, that we used to investigate oxygen gradients effects on hSV,[5] and more recently ii) a low-priming Petri-like 3D-printed system that we use to reproduce a reliable vascular thrombus *ex vivo* model.

Results

Results obtained with the Coronary-Hemodynamics system[6] revealed i) decrease of the intima and media thickness in CABG, ii) presence of endothelial cells (ECs, CD31 and vWF markers) in the luminal side with partial endothelial denudation, and iii) cell apoptosis in CABG. Recently, we used this system to study the role of relevant molecules in CABG-stimulated hSV, investigating the possible strain-dependent activation of adventitial resident progenitors (results not published yet).

Conclusions

Our experience shows that using bioengineering approaches facilitates the understanding of vascular physio-pathological mechanisms and, in perspective, will speed up the development of new life-saving treatments. The use of human samples, particularly OR-derived samples, which would have been otherwise discarded, is a very valuable approach. In line with the 3Rs principles, this methodology is worth the cost of being set up and managed, wherever and whenever possible.

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