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Supplement Aims and Scope

This supplement is intended to focus on drug eluting devices. Devices (eg cardiovascular stents, drug delivery biopolymers and tissue engineering devices), their biocompatibility, and mechanisms of transport are included within the supplement's scope.

Drug Target Insights aims to provide researchers working in this complex, quickly developing field with online, open access to highly relevant scholarly articles by leading international researchers. In a field where the literature is ever-expanding, researchers increasingly need access to up-to-date, high quality scholarly articles on areas of specific contemporary interest. This supplement aims to address this by presenting high-quality articles that allow readers to distinguish the signal from the noise. The editor in chief hopes that through this effort, practitioners and researchers will be aided in finding answers to some of the most complex and pressing issues of our time.

Introductory Editorial: Drug-Eluting Stents or Drug-Eluting Grafts? Insights from Proteomic Analysis

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The rapidly expanding panorama of prosthetic replacement and interventional procedures for cardiovascular disease demands significant research for the development of devices with optimized characteristics and performance to overcome the drawbacks of the existing strategies. Tissue engineering is a potent weapon in this scenario, enabling the realization of sophisticated biocompatible devices interacting with the host tissues and influencing their behavior. The fabrication and design of "smart" biomaterials, able to sense and interact with the biological milieu, represent a cornerstone in tissue engineering and regenerative medicine. This development has demolished the obsolete tenets of surgery implying reconstructing organs or part of them with artificial materials. The deeper understanding achieved by modern research has highlighted the limitations and the biological and clinical drawbacks of the long-term coexistence of a foreign material in the body, especially in the cardiovascular system.[1] The need to respect the physiological reparative and remodeling processes normally occurring in nature progressively achieved significance in the current research,[2,3] demonstrating the necessity to accompany the body's physiological responses and the activities of tissue regeneration rather than pretending to replace them with "plastic" surrogates. This attention to the biology of regeneration in tissue engineering and to micro-environmental conditions at the tissue and cellular levels is expressed in the articles of this special issue of *Drug Target Insights*. Interesting and sophisticated approaches are proposed in this context, entailing the use of drug-delivery

devices that release tailored compounds to target specific aspects of diseases or complications. In this issue, Dr Rapetto and colleagues extensively reviewed the role of gentamicin-impregnated collagen sponges (GICSs) in preventing sternal wound infection. The use of these delivery devices allows for topical delivery of high antibiotic concentrations to the wound, reducing the complications associated with gentamycin toxicity.[4] On the other side, alternative use of smart biopolymers able to release anticoagulant agents, such as heparin, to avoid early vascular graft thrombosis and failure will be presented and discussed in the same issue of the Journal.[5] These are not the only applications in this field, as demonstrated by other papers in this issue. Indeed, at the experimental level, several research efforts have been engaged in designing scaffold-releasing factors, drugs or cytokines to improve tissue regeneration or stem cell recruitment, or to overcome prosthesis-related issues.[6] The possibility to tailor a bioresorbable scaffold in order to create a microenvironment able to boost or guide tissue regeneration is an exciting area of investigation.[7,8] Additionally, drug-releasing devices might also allow avoidance or treatment of some of the drawbacks related to prosthetic replacement of cardiovascular structures.[5,6]

In the field of interventional cardiology there is a widespread use of drug-releasing stents, in particular of steroids or antiproliferative agents in order to prevent neointimal hyperplasia. Interestingly, the concept of paracrine or local release of molecules with modulatory or homeostatic action is not new in biology. Endothelium-mediated release of growth factors and regulatory molecules is a well-accepted natural mechanism to locally and remotely control or respond to a variety of physiological or pathological conditions, and different parts of the vascular tree might behave differently according to their biological needs. This concept has important ramifications also in the clinical side, especially when treating cardiovascular structures. Release of drug from coronary stents (drug-eluting stents, DES) able to influence or modify endothelial homeostasis and function is an example. More interestingly, the use of autologous non-artificial conduits in coronary artery bypass graft (CABG) surgery might be considered another intriguing system of "natural" drug delivery device. CABG might be performed using autologous saphenous vein or internal thoracic artery (ITA or mammary artery), two conduits with profoundly different biological features and structure. There is a general consensus on the accelerated degeneration of venous grafts after surgery, with extremely high incidence of failure and lower patency rates in comparison to arterial grafts. This difference in angiographic patency was shown to be associated with improved clinical outcomes and rates of ischemia-free survival in patients undergoing exclusive arterial revascularization, especially in case of subjects who previously developed in-stent restenosis.[9] Construction of coronary graft through the use of arterial conduits, especially with internal thoracic artery (ITA), is therefore advocated as desirable to ensure long-term patency and optimal clinical outcomes.[10,11]

The biological mechanisms underlying the poorer outcomes of venous grafts in respect to arterial ones are not well understood and still a matter of debate. Reduced production of nitric oxide has been claimed as a primary factor,[12] implicated in venous graft failure in relation to established risk factors for atherosclerosis;[13] also, differences in thrombin receptor expression between arterial and venous grafts have been demonstrated,[14] and deregulation of these receptors has been associated with in-stent restenosis.[15] Nitric oxide production is not reduced in arterial grafts and particularly the ITA, even with severe atherosclerotic disease, and this is thought to be one of the factors in the superior outcome of these conduits.[16] Additionally, it has been shown that the structure of the ITA itself is able to better adapt to arterial pressures and its endothelium responds to high flow rates with a higher amount of nitric oxide, providing superior reactivity to flow requirements in the coronary arteries when used as a graft in CABG.[17]

On this basis, ITA might be considered as a "drug-eluting" graft as it is able to release into the grafted myocardium nitric oxide, providing important signaling to prevent graft failure and ameliorate cardiac function. Clearly, the biology underlying this process is far more complex and is not restricted to a single compound, but most probably involves a wide spectrum of molecules interacting to determine the biological effects seen both experimentally and clinically.

Proteomics studies allow for a comprehensive analysis and identification of the complete protein pattern of a tissue or fluid,[18,19] and some studies performed using this approach showed the presence in human arterial smooth muscle of small leucine-rich proteoglycans involved in collagen fibrillogenesis, and of some non-fibrillar collagens in combination with alterations of several other proteins. This has been considered as a marker of arterial stiffness and therefore increased risk of developing atherosclerosis.[20] Structural proteomic studies on ITA tissue showed differential expression of proteins that are implicated in cytoskeleton activity regulation,[21] in the migrative capacity of vascular smooth muscle cells, extracellular matrix composition, coagulation, apoptosis, and heat shock response.[22] Interestingly, a proteomic analysis of the secrete of ITA, known as secretome, demonstrated an increased production of gelsolin, vinculin, lamin A/C and phosphoglucomutase 5 by mammary arterial tissues. These proteins are also involved in the regulation of important intracellular mechanisms related to cell migration, ECM deposition and smooth muscle phenotype switching, which are crucial steps in atherosclerosis pathogenesis.[23] The expression of specific groups of proteins in the ITA is claimed to be the basis of the relative protection of this vessel from the onset and progression of atherosclerosis, and subsequently of its beneficial effects when is used as a graft for coronary artery in terms of recurrence of heart disease.[22,23] From these studies, we might reliably speculate that when used in the context of CABG, the ITA exerts a "paracrine activity" liberating locally and within the blood stream factors that are able to maintain a positive

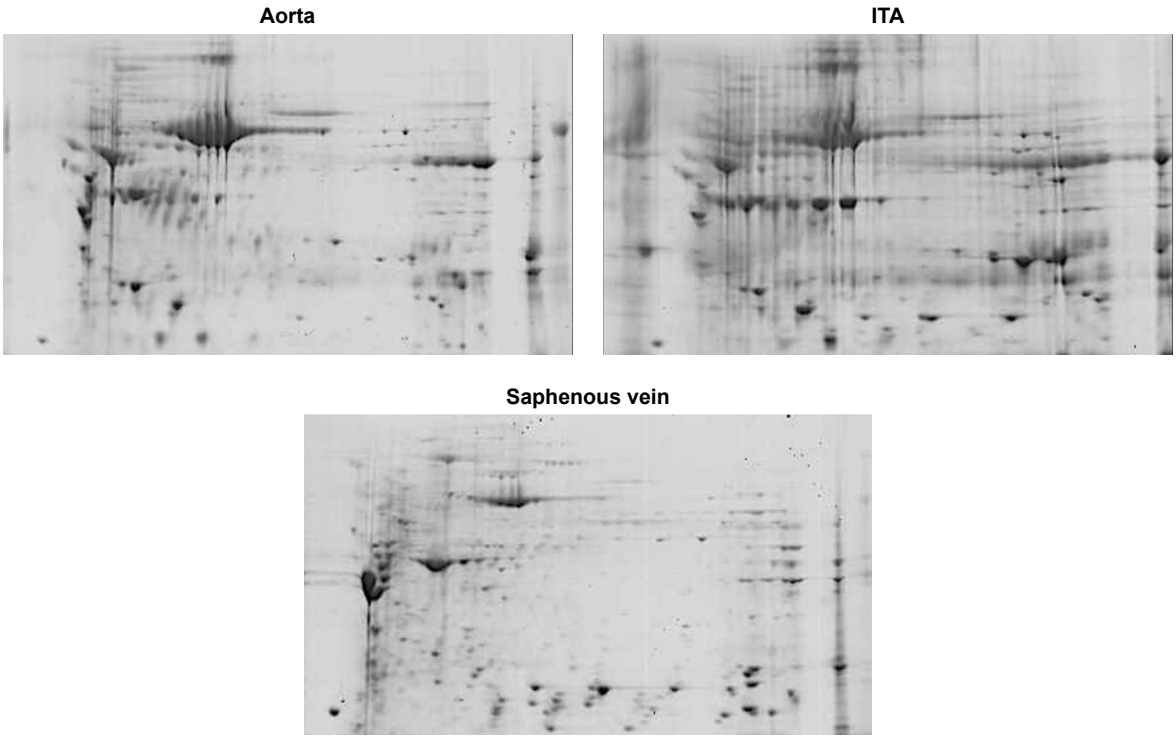

Figure 1. Comparison of proteomic profile of secreted proteins by saphenous vein graft, internal thoracic artery (ITA) and aorta.

vascular homeostasis, thereby avoiding disease recurrence in the grafted coronary and permitting high patency rate of the bypass in the long term. Considering the significant difference in patency rate when conduits different from ITA are used, more complex mechanisms should be underlying ITA selective advantage in CABG. Use of proteomics and redox-proteomics approaches to simultaneously compare the protein profile of ITA, saphenous vein grafts and aorta, another tissue prone to atherosclerosis, has been advocated to better understand differences among the conduits. Also, these investigations might be extended to the secretomes of these conduits in order to have a paracrine correlate to the targets found in the respective tissues. Differential profiles of protein expression exclusively present in ITA tissues and secrete, but not in the other vessels, have been intriguingly discovered (Fig. 1) and the identification of these proteins would provide in the future precious information to elucidate reasons of ITA superiority in CABG. Moreover, the identification of these proteins would enable more significant clinical applications. The factors produced by the ITA, and considered at the basis of the maintenance of graft patency and protection from atherosclerosis recurrence, might constitute in the future "drugs" to be administered to patients or eluted in stents or delivery devices. Conversely, factors identified from saphenous tissue, which are clinically associated to poor outcomes and failure of the grafts, might represent targets for design of specific compounds with inhibitory or blocking effects.

In the field of drug-eluting devices, a close observation and attention to the naturally occurring phenomena might provide us with a range of therapeutic options wider than any other drug currently used in DES or tissue engineering approaches. For example, the ITA naturally carries a regulated set of factors, finely modulated and intertwined, which protects against atherosclerosis and can be therefore considered the best drug-eluting device available at the moment in cardiovascular disease.

In conclusion, with the increase in life expectancy and in the morbidities related to chronic diseases, smarter weapons are required to control pathology. The exciting field of drug delivery devices might provide novel strategies and open new avenues in the treatment of cardiovascular disease. In this context, scientists might need to realize that the endogenous and physiologically-occurring release of paracrine factors by the native tissues might be a "system" to better understand and to target when constructing new drug-releasing devices.

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