Molecular mechanisms regulating perivascular adipose tissue – potential pharmacological targets?

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It is now over 25 years since the first study was published that identified a role for perivascular adipose tissue (PVAT) in the modulation of vascular function (Saltis & Cassis, 1991). The key observation in that study was that “intact” vessel rings in which the PVAT had not been removed exhibited a lower sensitivity to the adrenoceptor agonist noradrenaline. In some ways this parallels the discovery of the importance of the endothelium in modulating vascular function in that both were once routinely removed when researchers were preparing blood vessels for functional studies. Indeed, it has become clear that the endothelium and PVAT have a number of characteristics in common, the subject of a review by Zaborska et al in this issue (Zaborska et al., 2017). Both PVAT and the endothelium produce a wide variety of soluble mediators with paracrine functions that influence the underlying vascular smooth muscle cells (VSMCs). Furthermore, it is likely that PVAT-derived adipocytokines can influence not only the smooth muscle but also the vascular endothelium. Both PVAT and the endothelium generate the gasotransmitter nitric oxide (NO) and both can generate vasoactive molecules with seemingly opposing effects; probably as a counter-balancing or homeostatic system which can fine-tune the tone of the underlying VSMCs. Importantly, both the endothelium and PVAT can become dysfunctional with regard to their secretory profile and we are just beginning to appreciate (particularly in the case of PVAT), how important that can be in cardiovascular pathology; not only in CV diseases such as hypertension (Huang Cao et al., 2017) but in the pathogenesis of risk factors which predispose to cardiovascular disease such as obesity, type 2 diabetes mellitus and metabolic syndrome.

There are also important differences between PVAT and the endothelium. Unlike the endothelium, PVAT consists of multiple cell types. In addition to adipocytes, PVAT contains T-lymphocytes, macrophages, fibroblasts, preadipocytes in addition to blood vessels and nerves. Importantly, the infiltration of further leukocytes in certain pathologies is known to alter the PVAT secretory profile adversely in terms of the subsequent effects on vascular function and structure. Secondly, the type of PVAT can vary dependent on species and location in the vascular tree. Most PVAT depots resemble white adipose tissue, with adipocytes containing a large lipid droplet and relatively few mitochondria but some, such as rat and mouse aortic PVAT (Almabrouk et al 2017) contains a mixture of white and brown adipose tissue (Cinti et al., 2005) in which brown adipocytes contain multiple, smaller lipid droplets and high numbers of mitochondria. Interestingly, human coronary PVAT is slightly anomalous in that it is resembles white adipose tissue but with adipocytes of different size and differentiation state (Omar et al., 2014).

The complexity of PVAT in terms of its structure and the array of adipocytokines it releases has provided no shortage of challenges as we attempt to delineate its role in cardiovascular health and disease. However, it's a task worth undertaking and the accompanying reviews and articles published in this themed issue examine many facets of PVAT biology. A better understanding of how PVAT could offer new therapeutic strategies is reviewed by Akoumianakis et al in this issue (Akoumianakis et al., 2017). Such strategies could include not only modifying PVAT structure through diet, exercise or pharmacological intervention but also modulating release of PVAT-derived mediators, targeting inflamed PVAT and perhaps interfering with the cross-talk between PVAT and other layers of the vasculature. Whilst clearly much remains to be done, this timely themed issue in *British Journal of Pharmacology* will allow those working in this field to assess where we are and perhaps how we can best move our understanding forward. This themed issue presents 9 reviews and 4 original research papers in this area.

Not surprisingly, in view of the seemingly exponential increase in its incidence, several of the reviews in this themed issue deal with obesity and its consequences. The effects of obesity on PVAT function and the possible therapeutic targets that presents are reviewed by Xia and Li in this issue (Xia & Li, 2017). Furthermore, one target suggested is the enzyme AMP-activated protein kinase (AMPK), which is a critical regulator of cellular and whole body nutrient metabolism. The role of AMPK in PVAT is explored by Almabrouk et al in this issue, demonstrating that mice genetically engineered to lack one isoform of the catalytic subunit of AMPK have PVAT with dysfunctional anti-contractile activity (Almabrouk et al., 2017). Another potential therapeutic target is eNOS within the PVAT which is examined in this issue by Xia et al, who demonstrate dysfunctional PVAT eNOS in obese mice and that the dysfunction can be reversed by oral administration of a plant extract from the Hawthorn (Crataegus spp.) (Xia et al., 2017). PVAT has the ability to release, take up and metabolise noradrenaline and this "adrenergic" system is the subject of a review by Ayala-Lopez et al (Ayala-Lopez et al., 2017) in which consideration is given as to how the adrenergic system becomes dysfunctional in obesity and whether it represents a viable therapeutic target.

A mainstay of preventing CV disease is to encourage exercise and the interactions between muscle (both smooth and skeletal) and PVAT are also reviewed by Boa et al in this issue (Boa et al., 2017). Myokines generated by exercising muscle have been reported to improve the PVAT phenotype by increasing insulin sensitivity and "browning" the adipocytes, indicating that it is not only a reduction in total adiposity in response to exercise which is beneficial.

Inflammation within PVAT appears to be central to blood vessel dysfunction and is apparent in diseased vessels. A consequence of increased pro-inflammatory signalling within PVAT is the generation of not only chemokines but also oxidative stress within the tissue. Under such conditions, there may be a switch from a net anti-contractile to a pro-contractile effect of PVAT, as reviewed by Ramirez et al in this issue (Ramirez et al., 2017). Furthermore, the balance between pro-inflammatory mediators such as TNF-α, IL-1β and IL-6 and anti-

inflammatory mediators such as adiponectin within the PVAT is altered in vascular disease and is discussed in this issue by Nosalski and Guzik (Nosalski & Guzik, 2017). Over the previous few years, it has become apparent that PVAT-derived adiponectin may represent a key mediator of the anti-contractile action of PVAT. In support of this, a study in this issue by Sena et al illustrates that chronic infusion of adiponectin in rats fed a high fat diet not only reduced body weight, but also improved insulin sensitivity, reduced expression of inflammatory adipocytokines in the PVAT and normalised NO-dependent vasodilation (Sena et al 2017). Paradoxically, although adiponectin has anti-inflammatory, antioxidant and vasodilator roles (Almabrouk et al., 2017; Sena et al., 2017), levels of adiponectin are increased in patients with CV disease; possibly as a mechanism to normalise the pathophysiology. Recently, adipoRon, a small molecule adiponectin receptor agonist has been showing promise in animal models of ischaemia-reperfusion (Zhang et al., 2015).

Generation of reactive oxygen species (ROS) not only decreases NO bioavailability by direct sequestration and formation of peroxynitrite, but can also cause eNOS to become dysfunctional in other layers of the vessel. Indeed, a clear link between loss of anti-contractile activity in obese murine aortic PVAT and increased mitochondrial ROS in the PVAT is shown by da Costa et al in this issue (da Costa et al., 2017). Interestingly, in their study, obese mice lacking the TNFα receptor were protected from the deleterious effects of the high fat diet on PVAT function. This study is interesting in that it links a specific cytokine known to be upregulated in inflamed PVAT with a measurable effect on vessel function and further strengthens the link between PVAT inflammation and vessel dysfunction.

Epicardial fat represents a small depot of fat but of course, due to its location and ability to exert paracrine effects on both cardiac myocytes and the coronary artery wall, it is of great interest. In animal models, pericardial fat is scare and difficult to study and the review by Rietdorf and McQueen in this issue addresses this by examining some experimental methodologies such as co-culture of adipocytes and cardiac myocytes which may overcome some of these difficulties (Rietdorf & MacQueen, 2017). Studies have demonstrated that the amount of epicardial adipose tissue predicts outcome of some cardiological interventions and also the incidence of coronary artery disease. Contrast this with the protective role of the PVAT surrounding saphenous vein grafts presented in the review by Fernandez-Alfonso et al (Fernandez-Alfonso et al., 2017). When harvested as part of the “no-touch” technique, the saphenous PVAT protects the graft; probably not only by protecting it from the higher pressures encountered when the vein is grafted into the arterial circulation but also by paracrine signalling which may help the graft adapt structurally to its new role.

Our knowledge of the function of PVAT in health and disease is moving forward, but as a heterogeneous tissue capable of releasing myriad biologically active substances and dramatically altering its structure and function in disease states, it will certainly be an active topic of research for quite some time. Perhaps the most exciting aspect of PVAT is the therapeutic targets it will undoubtedly offer. Obesity is a worldwide epidemic, increasing

risk of cardiometabolic diseases and altering PVAT. Development of a drug which can reduce or prevent the deleterious effect of PVAT in disease states may be just as significant as the stains were in lowering LDL levels.

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