On the environmental stress that reshapes our vessels

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This editorial refers to ‘Pregnane X receptor regulates drug metabolism and transport in the vasculature and protects from oxidative stress’ by K.E. Swales et al., pp. 674–681, this issue.

Adaptation to environmental stress is key to animal survival. Humans, however, are temporarily above some of the consequences of the environmental stress by the use of vaccines, antibiotics, and organ transplantation; they are, however, not totally immune to their environment. The fundamental questions are (i) how do we detect the environmental stress and (ii) how do we adapt to it?

Stress comes in a multitude of flavours. The classical risk factors for cardiovascular diseases are by definition deleterious, but the vessels certainly tentatively adapt to them.1 An intermittent low level of ischaemia generated by exercise2 and during ischaemic preconditioning3 is another type of stress that activates defence and repair pathways and that is beneficial to the cardiovascular system. While our lifestyle shapes our metabolism and overall biology, most cell types express receptors that sense chemicals, natural or not, contained in what we ingest and what we breathe. The ensuing signals modify the cells, making certain that they are able to appropriately use these chemicals as well as to resist to their toxicity if needed. Overall, these responses, also known as hormetic responses, are mid- to long-term adaptive and protective molecular changes to low- to medium-level environmental stress4 and have the ability to influence longevity by improving stress resistance5 and, thus, delaying damage. Hormesis does not trigger the expression of de novo pathways but rather reinforces existing pathways.

Although we are far from understanding the mechanisms associated with these environmental adaptations, we know that many of the environmental chemical signals are transduced by non-specific nuclear receptors.6 The pregnane X receptor (PXR; also known as steroid and xenobiotic receptor) is a non-specific nuclear receptor activated by endogenous hormones, dietary steroids, drugs, and xenobiotic compounds.6–9 PXR is a sensor regulating clearance via induction of genes involved in drug and xenobiotic metabolisms, including transport (multidrug resistance 1 or MDR1), conjugation (glutathione transferase) and oxidation (cytochrome P450 or CYP, glutathione peroxidase). Swales et al.10 elegantly demonstrate that the expression of PXR in human vascular smooth muscle and endothelial cells has potential physiological consequences leading, upon activation, to the induction of MDR1, CYP3A, CYP2B, and CYP2C as well as to the increase in cellular levels of glutathione and in glutathione peroxidase activity. These changes are in agreement with the known activity of the PXR in the liver.7 Consequently, as shown in this study, PXR not only can activate pro-drugs such as clopidogrel to generate the active P2Y12 ADP receptor antagonist but can also stimulate defence mechanisms against oxidative stress, promoting cell survival.

Our vascular cells and macrophages express many other non-specific nuclear receptors. The liver X receptor and peroxisome proliferator-activated receptors are key regulators of lipid homeostasis and inflammation and play important roles in atherosclerosis development.11,12 The constitutive androstane receptor and the aryl hydrocarbon receptor (AhR) link diet to toxicity and immunity by being involved in the bioactivation, detoxification, and transport of various drugs, xenobiotics, endogenous substances (e.g. bilirubin, bile acid, and various vitamins), and environmental toxins.7,13 As such, all these nuclear receptors have the potential to be instrumental in modulating various physiological and pathophysiological processes.

Why is the work of Swales et al. so important? As mentioned by the authors, up-regulation of CYP should influence vascular reactivity and resistance to stress.14,15 Chronic PXR stimulation could also reshape the transcriptome of our vessels in depth. For example, cholesterol binds to PXR; we reported that in a mouse model of mild dyslipidaemia, the activity of the endothelium-derived hyperpolarizing factor (known to be CYP2C9-dependent15) is prematurely up-regulated early in life but vanishes with age,1,16 demonstrating that the vascular system adapts to a potentially stressful environment which was not sustainable in this mouse model. Another example comes from the use of the polyphenol catechin whose intake is known to be protective and reduce cardiovascular events.17 Intuitively, we think that the protection must be dependent on its antioxidant properties; catechins, however, bind to PXR.5 Could the chronic effects of catechins be independent of their antioxidant properties and associated with the up-regulation of antioxidant enzymes or other proteins, as previously shown?18 Could activation of PXR by catechins lead to the long-term regulation of gene expression through epigenetic modifications,

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The modulatory role of nuclear receptors (NRc). This schematic tentatively represents the environment in which nuclear receptors could influence the normal function of an effector cell (myocyte, neuron, hepatocyte, adipocyte, immune cell, etc.) and an endothelial cell (EC). Because 90% of the oxygen is used in the mitochondria (Mito), reactive oxygen species (simply represented by H2O2) are important signalling molecules maintaining physiological functions. For example, H2O2 activates Akt and PGC1α: this sustains the activity of defence pathways such as those regulated by Nrf2 and heat shock factors (HSF). Activation of nuclear receptors by xenobiotics, chemicals, and metabolites modulate these pathways, depending on the level of activation. They could reinforce defence systems and immunity, i.e. have a hormetic action. Of course, abnormal, high levels of activation of nuclear receptors may be toxic. VSMC, vascular smooth muscle cell; NO, nitric oxide; see text for further abbreviations.

References
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