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EDITORIAL

Vascular smooth muscle cells and monocyte–macrophages accomplice in the accelerated atherosclerosis of insulin resistance states

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This editorial refers to 'Insulin resistance aggravates atherosclerosis by reducing vascular smooth muscle cell survival and increasing CX_3CL1/CX_3CR1 axis' by S. Martínez-Hervás *et al.*, pp. 324–336, this issue.

The mechanisms driving accelerated atherosclerosis in insulin-resistant (IR) conditions, such as Type 2 diabetes and the metabolic syndrome, are incompletely understood. Clarifying such pathways is of paramount importance in view of the epidemic spread of obesity and diabetes, and in order to devise novel therapeutic approaches to counter cardiovascular disease globally. IR develops classically in metabolically active tissues (such as the liver, muscle, and fat), but the vasculature can also show signs of IR,[1] with impairment in the Erk and Akt pathways.

Many cell types are involved in the atherogenetic process and complex cross-talks take place within the atherosclerotic plaque. Vascular smooth muscle cells (VSMCs) and monocyte–macrophage lineage cells are two major players provided with both protective and pathogenic functions. VSMC proliferation promotes plaque growth, but also forms the fibrous cap of the atheroma, a thick and resistant shield against plaque rupture and thrombosis. However, VSMCs from human atherosclerotic vessels are senescent and intrinsically prone to apoptosis.[2,3] In fact, when VSMCs undergo apoptosis, atherosclerosis accelerates, and plaques become unstable[4,5] and calcific.[6] Vice versa, inhibition of apoptosis blunts the atherosclerotic process.[7] This finely tuned balance between VSMC proliferation and death is a key determinant of atheroma progression.[8]

Monocyte–macrophage cells can exist in two distinct states with opposing effects on atherosclerosis.[9] According to the pattern of local stimuli, macrophages can be polarized towards a pro-inflammatory (M1) phenotype prone to foam cell differentiation,[10] or towards an anti-inflammatory (M2) phenotype with scavenger activity.[11] The M1/M2 polarization balance of plaque macrophages and blood monocytes reflect pro-/anti-atherosclerotic conditions. Interestingly, IR primes M1 monocyte–macrophages,[12] while countering IR with peroxisome proliferator activating receptor-gamma activation can restore the M1/M2 balance.[13]

In this issue of *Cardiovascular Research*, Martínez-Hervás *et al.*[14] show that inducing IR in VSMCs by knocking down insulin receptor substrate-2 (IRS2) stimulates a CX_3CL1/CX_3CR1 autocrine/paracrine loop and induces VSMC apoptosis, which is reflected *in vivo* by the development of unstable plaque features. Both the Akt and Erk pathways were likely involved in up-regulating the CX_3CL1/CX_3CR1 axis induced by IR *in vitro*. As the treatment of VSMC with CX_3CL1 in the presence of oxidant conditions or IR increased apoptosis, it is possible that the CX_3CL1/CX_3CR1 axis is indeed mechanistically linked to the VSMC apoptosis seen in IR. However, this pathogenic pathway awaits definite confirmation by experiments that block fractalkine (CX_3CL1) binding to its receptor CX_3CR1, which should blunt VSMC apoptosis and decelerate atherosclerosis in models of IR. Although genetic and pharmacological blockade of CX_3CR1 reduces atherosclerosis in the $ApoE^{-/-}$ or $LDLr^{-/-}$ mice,[15,16] the exact mechanism is unclear and data also suggest that CX_3CL1 may be anti- rather than pro-apoptotic for both VSMCs[17] and monocytes.[18] While the activity of CX_3CL1 in inducing monocyte recruitment into the vessel wall via binding to CX_3CR1 is well established, the deleterious role of CX_3CR1 expression on monocyte–macrophage cells is debatable, as CX_3CR1 is traditionally considered a marker of circulating M2-like cells that patrol the vessel walls.[9] Consistently with this patrolling role, CX_3CR1 is rapidly down-regulated upon monocyte-to-macrophage differentiation[19] and its role in tissue macrophage function is unknown. Circulating CX_3CR1^+ $CD206^+/CD163^+$ M2 monocyte–macrophages were shown to be reduced in Type 2 diabetic patients, compared with controls,[20] though CX_3CR1 expression *per se* was unaffected. Interestingly, Martínez-Hervás *et al.* now show that peripheral blood mononuclear cell (PBMC) CX_3CR1 gene expression is increased in patients with the metabolic syndrome compared with controls and positively correlates with IR and carotid intima-media thickness.[14] The IR–CX_3CL1/CX_3CR1 pathway described by Martínez-Hervás *et al.* is supposed to act intrinsically in VSMCs, while the role of monocyte–macrophages in this model is unclear. It can be speculated that CX_3CR1 expression on monocytes interacts with VSMC-derived CX_3CL1 to amplify the atherosclerotic process.

In biomedical research, the study of tissue-specific pathways if often replicated exploring patients' PBMC gene expression.[21] The translational nature of this mouse-to-human approach (*Figure 1*) is important as it provides preliminary evidence that the identified pathway may be working

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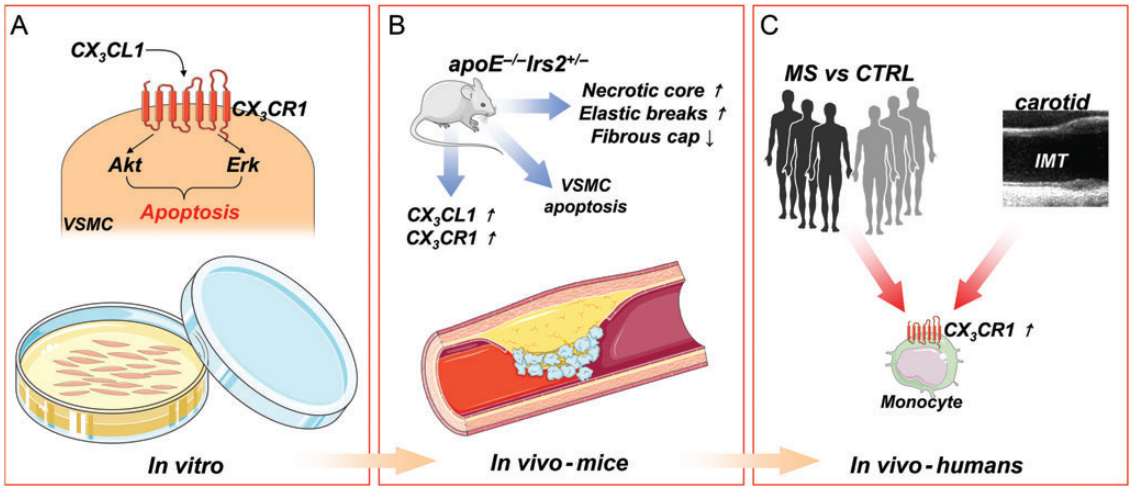

Figure 1 The translational approach used to demonstrate the role of CX_3CL1/CX_3CR1 in VSMCs and monocytes, in the setting of IR states, such as the metabolic syndrome. (*A*) IR VSMCs undergo dysfunction and apoptosis via the CX_3CL1/CX_3CR1 axis. (*B*) Insulin resistance induced by Irs2 haploinsufficiency in $ApoE^{-/-}$ mice induces unstable plaque features with concomitant vascular CX_3CL1/CX_3CR1 up-regulation. (*C*) Monocyte CX_3CR1 expression is increased in metabolic syndrome (MS) patients compared with controls (CTRL) and correlates with vascular remodelling, measured as carotid intima-media thickness (IMT).

also in humans. However, transferability of findings obtained in patients' PBMC to very different cellular models, such as human VSMC, may be problematic. Beyond the simple parallelism between cell types and the use of PBMC as surrogates/mirrors of pathological processes ongoing elsewhere, it is intriguing that monocytic CX_3CR1 might be pathophysiologically involved in IR-induced atherosclerosis. Notwithstanding this general limitation, the novel data presented in the current issue of *Cardiovascular Research* provide intriguing evidence on the interplay between VSMCs and monocyte–macrophages in the accelerated atherosclerotic process induced by IR, through a common pathway driven by the CX_3CL1/CX_3CR1 axis. This mechanism should be pursued as a therapeutic target against IR-associated cardiovascular disease.

Conflict of interest: none declared.

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