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Commentary

Markers of Apoptosis Predict Cardiovascular Outcomes and Point to 'Response to Injury' as a Common Pathway Leading to Diabetes and Cardiovascular Events

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Metabolic stress, chronic vascular injury and cellular apoptosis are considered as instrumentally connected in the pathogenesis of atherosclerosis and diabetes (Gistera and Hansson, 2017). The work from Mattisson et al. (Mattisson et al., 2017) sheds light on this potentially important pathway linking cell-mediated death and cardiovascular outcomes. The study spans translational science, from describing an elegant laboratory technique using Fas ligand to induce apoptosis in peripheral blood mononuclear cells and demonstrating release of TNF receptor 1 (TNFR-1), TNF-related apoptosis-inducing ligand receptor 2 (TRAILR-2) and Fas, to studying the cell death receptor plasma levels in a large well-characterized prospective population.

The initial experiment demonstrated the link between ligand-induced apoptosis in cells, and the release of soluble receptors for Fas, TNFR-1 and TRAILR-2 *in vitro*, thus justifying the future measurement of levels of soluble receptors as clinical biomarkers relating to apoptosis.

The authors took the study forward in a subset of the Malmo Diet and Cancer Study (Berglund et al., 1993), with an impressive follow up period. This part of the study demonstrated that several cardiovascular classical risk factors (age, high body mass index, smoking and hypertension) as well as high triglycerides and low levels of high density lipoprotein, correlated with the studied markers of death receptor-activated apoptosis. Furthermore, the highest tertiles for all three soluble cellular death markers predicted which patients would go on to develop diabetes, with TRAILR-2 having an independent association after correction for other risk factors. In addition, patients with known diabetes exhibited raised levels of markers of receptor-activated apoptosis. Aside from predicting incident diabetes, the highest levels of TRAILR-2 also independently predicted future cardiovascular death, incident myocardial infarction and stroke.

It has become clear that metabolic risk factors and other exogenous causes of cellular stress lead to detrimental clinical events *via* multiple pathways (Ceriello and Motz, 2004). This paper shows that *in vitro* cellular stress on peripheral blood mononuclear cells and a pancreatic beta cell line leads to the release of soluble death receptors. The mechanism for death receptor release remains to be determined, but could include either proteolytic cleavage or the budding off of membrane microparticles during apoptosis.

Although the mechanistic work *in vitro* demonstrates a clear link between the death receptors and apoptosis, and the clinical study demonstrates an association with cardiovascular outcomes, a causal link cannot be conclusively proved. Moreover, presently we cannot be sure what cells released the death receptors into the clinical sample plasma – although, if microparticle formation is involved, it may be possible in due course to define their origin by dual staining with lineage markers. That said, the value of having a biomarker that may indicate whether a risk factor has induced cellular damage or not, is strikingly clear. This may well provide a method of validating difficult to establish risk factors such as smoking, and may aid in the enrolment of patients for randomized controlled studies. Rather than just rely on reported classical risk factors, one may choose to measure soluble death receptor levels as entry criteria for prospective studies requiring patients at high risk of cardiovascular outcomes. In addition, the presence of high death receptor levels could aid in the selection of high risk patient populations for novel drug therapies (Ridker et al., 2017), and in particular for therapies that target the 'response to injury' pathway (the response to cellular injury caused by metabolic or oxidative stress leading to pathology including atherosclerosis), such as with immunization (Grasset et al., 2015).

In non-diabetics, levels of these receptors, in particular TRAILR-2, were associated with the development of diabetes on follow-up. This gives some plausible support to the controversial notion of loss of beta-cells in diabetes being a consequence of metabolic stress inducing cell-driven apoptosis (Halban et al., 2014). There is further value here in suggesting that measuring TRAILR-2 (if confirmed in other studies) may aid in the selection of patients for diabetic prevention measures, such as dietary interventions, or even novel drugs that may aim to preserve beta-cell function.

The authors also undertook a genome-wide association study using existing databases, and demonstrated a few links with single nucleotide polymorphisms. However, the genetic polymorphisms linked to plasma levels of soluble death receptors seem to have a limited effect on cardiovascular risk. Therefore, it is likely that the levels of soluble death receptors, although being partially dependent on genetics, are unlikely to play a causal role in the development of cardiovascular disease. Nonetheless, they can serve as useful biomarkers of disease status, rather than therapeutic targets in themselves.

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It may well be that 'response to injury' is a central pathway for the development of atherosclerosis. For example, the accumulation of lipoprotein-derived lipids in the artery wall may cause injury and drive apoptosis, but the process is likely to be policed by the humoral immune system, therefore preventing a vicious cycle of further injury and cell death (Khamis et al., 2016; Wang et al., 2016). The levels of soluble cell death receptors may have some correlation with the robustness of these host defenses, and this could present a further avenue for study. The potential dynamism of levels of the soluble receptors also needs to be established, to elucidate for example if levels alter with secondary cardiovascular prevention medications.

It is clear from this work that there may be a role for measuring soluble death-receptor levels to sub-select patients at risk of diabetes and cardiovascular disease, and target them for early intervention as well as novel treatments. Once these findings are confirmed in other cohorts, some of the receptor levels may also find themselves in risk stratification matrices that select patients for aggressive cardiovascular and diabetes prevention measures, as well as permitting monitoring of the efficacy of these interventions.

Disclosure

The authors declared no conflicts of interest.

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