ADAM-15 and glycocalyx shedding: a new perspective on sepsis-related vasomotor dysfunction

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This editorial refers to ‘A disintegrin and metalloproteinase 15-mediated glycocalyx shedding contributes to vascular leakage during inflammation’ by Y. Yang et al., pp. 1752–1763.

Septic shock represents an ongoing clinical conundrum, with high mortality rates despite the usual background of extensive haemodynamic support and multiple foci of therapeutic endeavour. A prominent clinical feature in such cases is the appearance of extensive fluid extravasation, contributing not only to ‘non-haemodynamic’ pulmonary oedema, but also to further impairment of haemodynamics and of respiratory gas exchange. Impairment of left ventricular systolic function and of renal function also is observed frequently, as patients enter a ‘downhill spiral’.

A major contributor to this deterioration is inflammatory erosion of the endothelial glycocalyx. Depletion of any of the proteoglycan or glycoprotein components of the glycocalyx is likely to result in increased permeability of endothelial cells to both fluid and leucocytes/monocytes, as well as platelet aggregation and development of non-laminar flow and resultant accentuation of inflammatory responses. Apart from sepsis, ‘glycocalyx shedding’ (GS) has been associated with a large number of disease states, including acute myocardial infarction and diabetic nephropathy. The list of ‘sheddases’ implicated as precipitants of GS is increasing (see Table 1) and includes not only catecholamines, B-type natriuretic peptide and peroxynitrite, but several enzymes, especially matrix metalloproteinases (MMP). To date, no treatment has been validated clinically as a ‘broad-spectrum’ inhibitor of sheddase activation. Preliminary data suggest that low-dose doxycycline represents a non-specific MMP inhibitor, but clinical evidence of its efficacy in sepsis and other acute GS-associated disorders is minimal at this stage.

Yang et al. revisit evidence that ADAM-15, a disintegrin and metalloproteinase, is involved in the pathogenesis of GS induced by sepsis. The investigators detected increased plasma CD44 ectodomain concentrations after caecal ligation and puncture-induced sepsis in a mouse model and were able to attribute the cleavage of CD44 (thus releasing its ectodomain into plasma) to ADAM-15. In turn, in a cell culture model, transendothelial electric resistance was reduced by exogenous CD44 ectodomain, resulting in cell–cell adherence junction disorganization. Thus a ‘two-step’ process of GS, initiated by ADAM-15, and exacerbated by CD44 ectodomain, was delineated. Furthermore, the presence of this cascade was confirmed both in the isolated cell model and ADAM-15-/- mice. Finally, in isolated intact human lung, ADAM-15 was significantly up-regulated by lipopolysaccharide perfusion and at the same time, increased CD44 was detected in the effluent, while vascular permeability to albumin was increased.

These results therefore suggest that ADAM-15 contributes substantially, but not exclusively, to the pathogenesis of GS in sepsis, and therefore, to the loss of barrier function implicit in this process. This delineation of a deleterious cascade involving both ADAM-15 and the shed ectodomain of CD44 represents a totally new mechanism for self-accelerating glycocalyx damage.

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Table 1 Perspectives of glycocalyx shedding: disease states, candidate ‘sheddases’, and potential plasma markers

<table>
<thead>
<tr>
<th>Disease states</th>
<th>Ischaemia/hypoxia/myocardial infarction, CABG, sepsis, inflammation, diabetes, atherosclerosis, renal disease, haemorrhagic viral infections, tumour invasion/metastasis, Alzheimer’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidate sheddases</td>
<td>Nucleosides (adenosine and inosine); proteases, cytokines and chemokines; peroxynitrite; thrombin; plasmin; elastase; tryptase and cathepsin B, natriuretic peptides: ANP, BNP, CNP, matrix metalloproteases, ADAM family, BACE protein family</td>
</tr>
<tr>
<td>Plasma markers</td>
<td>SD1, SD4, heparan sulfate, hyaluronic acid, chondroitin sulfate</td>
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</tbody>
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*Sheddases* are listed independent of suggested disease-related roles.

ADAM, A disintegrin and metalloproteinase; ANP, A-type natriuretic peptide; BACE, β-site amyloid precursor protein cleaving enzyme; BNP, B-type natriuretic peptide; CNP, C-type natriuretic peptide; CABG, coronary artery bypass grafting; SD, syndecan.
However, a number of important residual issues and, indeed, caveats, arise from these important findings. For example, there is little current information about either the mechanism(s) underlying physiological, as distinct from pathological, glycocalyx turnover. Given that differing ‘shedases’ may have selective impacts on various components of the glycocalyx, it can no longer be assumed that the pathophysiological impact of all forms of GS is similar, irrespective of potentially differential targeting of glycocalyx components. Most importantly, as recognized by the authors, the relationship between GS and derangement of the various components of endothelial cell function, including nitric oxide signalling, remains essentially unexplored.

In conclusion, the recent report from Yang et al.10 is potentially very important, and certainly represents a new slant on GS. As such, it merits extensive follow-up investigations, not only to ascertain its full physiological impact in the mouse models used in the current study but also to determine whether it modulates GS in other circumstances.

The final question is always of potential clinical utility. To date, ADAM-15 has been implicated largely in the setting of carcinogenesis. Recombinant human disintegrin domain of ADAM-15 has been shown to have anti-tumour and anti-angiogenic activity.11 Increased ADAM-15 has also been reported in lung inflammation,12 atherogenesis,13 as well as rheumatoid arthritis.14

There is currently no convenient method to suppress the ADAM-15/CD44 cascade in humans. Endogenous tissue inhibitors of metalloproteinases modulate the enzymatic activity of the ADAMs and may be effective on selectively inhibiting ADAMs.15 This interaction should now be specifically evaluated regarding ADAM-15.

These new insights serve once more to remind us that ‘endothelial dysfunction’ is a very imprecise term, and that a sick glycocalyx equates to sick vascular endothelium. The search for cures for endothelial dysfunction needs to embrace specific pathogenetic pathways.

Conflict of interest: none declared.

References