**Insight** GPI-anchored uPAR relies on two partners to trigger selected signal transduction events

**Two signalling hands for uPAR**

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Transmembrane proteins usually relay signals to the cytoplasm and nucleus via their intracellular domains. Nonetheless, this paradigm is challenged by glycosylphosphatidylinositol (GPI)-anchored proteins. Although completely extracellular, these proteins are linked to the lipid bilayer of membranes by a chemical bond between their C-terminal end and the glycolipidic GPI membrane component. Despite the absence of a transmembrane domain, a large number of GPI-anchored proteins are known to bind ligands and trigger intracellular responses.

An example is the urokinase-type plasminogen activator receptor (uPAR), a molecule involved in cell adhesion, migration and invasion, potentially representing a key player in cancer metastasis (1). While this protein is thought to localise its ligand, the uPA protease, to specific pericellular locations, uPAR also evokes selected intracellular responses promoting cell migration and invasion. The mechanism of these processes has only recently started to emerge (2). For example, in this issue of *Thrombosis and Haemostasis*, Montuori and colleagues show that the GPI-anchored uPAR relies on two partners to trigger selected signal transduction events (3). uPAR was found to trigger the Erk1/2 and p38 MAPK pathways through direct activation of both integrins and G protein-coupled receptors of the fMLF receptor family. One domain of uPAR binds to integrins and triggers their activation, another binds to fMLF receptors and acts as a ligand to induce activation of the heterotrimeric G protein Gi.

Interestingly, Montuori et al. observe that activation of both of these two signalling branches is required to trigger a full scale intracellular response, leading to uPA production and secretion through Erk1/2 activation. Triggering of this autocrine loop is found to occur in different cancer cell lines where it might enhance and sustain uPA production (3). It is thus possible that this mechanism contributes to the matrix remodelling and signalling aberrations known to support cancer growth and invasion. Therefore, blocking uPAR signalling might represent a potential treatment against cancer progression and further studies in this field might open new ways for targeted treatments.

**Conflicts of interest**
None declared.

**References**