Regulation of annexin A2 and S100A10 expression on the endothelial cell surface

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Annexin A2 (A2) and its binding partner S100A10 (p11) form a heterotetrameric complex on the surface of vascular endothelial cells. This complex interacts with plasminogen and its endothelial cell-derived activator, tissue plasminogen activator (tPA), enhancing the catalytic efficiency of plasmin generation. Complete absence of A2 leads to a prothrombotic diathesis and angiogenic defects in mice. We have hypothesized that translocation of A2 from the cytoplasmic compartment to the endothelial cell surface is a dynamic process that regulates plasmin activation during periods of vascular stress or injury. Translocation of this "signal-less" protein follows brief temperature stress or stimulation with thrombin, and does not require an intact endoplasmic reticulum. The process involves src kinase mediated phosphorylation of A2 at tyrosine 23, and absolutely requires expression of p11. Interestingly, p11 is expressed at very low levels in A2-null cells both *in vivo* and *in vitro*. In the absence of A2 in the endothelial cell, unpartnered p11 becomes polyubiquitinated and rapidly degraded via a proteasome-dependent mechanism. A2 stabilizes intracellular p11 through direct binding, thus masking an autonomous polyubiquitination signal on p11 that triggers its destruction. This mechanism prevents accumulation of free p11 within the endothelial cell and suggests that regulation of tPA-dependent cell surface fibrinolytic activity is precisely tuned to the intracellular level of p11. These data suggest that A2 and p11 fulfill distinct, but related roles in regulating activation of plasmin and associated proteolytic cascades.