The unfolded protein response controls induction and activation of ADAM17/TACE by severe hypoxia and ER stress.

Abstract:
The family of ADAM (a disintegrin and metalloproteinase) proteins has been implicated in tumor initiation and progression. ADAM17/tumor necrosis factor-α (TNFα)-converting enzyme (TACE) has been initially recognized to release TNFα as well as its receptors (TNFRs) from the membrane. ADAM17, TNFα and TNFR have been found upregulated in cancer patients, although the underlying mechanisms remain largely unknown. As hypoxia is a hallmark of cancer that can lead to severe stress conditions accumulating in endoplasmic reticulum (ER) stress and the unfolded protein response (UPR), we investigated the role of these stress conditions in the regulation of ADAM17 and release of TNFR1. We found that severe hypoxia induced ADAM17 expression and activity. Although hypoxia-inducible factor 1α (HIF1α) was important to maintain basal ADAM17 mRNA levels during moderate hypoxia, it was not sufficient to induce ADAM17 levels under severe hypoxia. Instead, we found that ADAM17 induction by severe hypoxia can be mimicked by ER stressors such as Thapsigargin and occurs as a consequence of the activation of the PERK/eIF2α/ATF4 and activating transcription factor 6 (ATF6) arms of UPR in several tumor cell lines. ADAM17 expression was also increased in xenografts displaying ER stress because of treatment with the vascular endothelial growth factor (VEGF) inhibitory
antibody Bevacizumab. Additionally, severe hypoxia and ER stress activated ADAM17 and ectodomain shedding of TNFR1 involving mitogen-activated protein (MAP) kinases and reactive oxygen species (ROS). Collectively, these results show that ADAM17 is a novel UPR-regulated gene in response to severe hypoxia and ER stress, which is actively involved in the release of TNFR1 under these conditions. These data provide a novel link between severe hypoxic stress conditions and inflammation in the tumor environment.