

Unfolded protein response (UPR) signalling in anti-angiogenic therapy for patients with breast cancer resistance to current anti-VEGF agents

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Tumour growth requires nutrients and oxygen as well as an ability to evacuate metabolic waste and CO₂. In order to meet these needs, angiogenic switch is activated, leading to newly formation of vessels from the existing host vasculature. Sustained aberrant tumor angiogenesis plays a central role in breast cancer carcinogenesis and metastatic potential. Members of vascular endothelial growth factor (VEGF) family are well-known angiogenesis activators. Despite the promising activity of anti-VEGF agents in preclinical settings, these drugs appear to be insufficient for inhibiting tumor angiogenesis in breast cancer patients. There remains an urgent and unmet need for novel targets therapies for patients with resistance to current anti-VEGF agents. Our previous study suggested that under the stress conditions caused by tumor microenvironment or/and anti-VEGF therapies, activation of the unfolded protein response (UPR) proteins of the endothelial cells contributes to maintenance of the intracrine VEGF levels in the endothelial cells. Here, we identified that self-complementary adeno-associated virus serotype 2 (scAAV2) vectors containing 7 surface exposed tyrosine to phenylalanine capsid mutations was able to transduce microvascular endothelial cells with high efficiency. scAAV2 septuplet-tyrosine mutant vectors encoding the siRNAs against UPR proteins including IRE1 α or XBP-1 or ATF6 significantly inhibited breast cancer-induced angiogenesis in vitro by, in part, inhibiting endothelial cell survival. Acoustic-resolution photoacoustic microscopy (ARPAM) can provide non-invasive, label-free, high resolution vascular imaging. Utilizing ARAM, we showed that intratumoral delivering the siRNAs against IRE1 α or XBP-1 or ATF6 by scAAV2 septuplet-tyrosine mutant vector resulted in a significant decrease in tumor growth and tumor angiogenesis in breast cancer xenograft models.

Biography

Jun Cai received his M.D. in Neurology from Shanghai No.2 Medical University in China. He completed his Ph.D. from the University of Wales College of Medicine, UK, investigating cancer metastasis and tumour angiogenesis. He his expertise is in the area of VEGF signaling. His research over the last decade has been advancing the field of regulatory role of VEGF in pathological settings. He has recently expanded his study to tumour microenvironment.

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