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Therapeutically targeting angiogenesis: Characteristics of tumor-associated endothelial cells and a new mechanism of resistance to bevacizumab

Tumor-associated endothelial cells express unique markers and exhibit differences in blood vessel structure, permeability, internalization of monoclonal antibodies (mAbs), and transcytosis as compared to normal organ endothelial cells. In tumors, endothelial cells are near cancer stem-like cells (CSCs) or tumor cells. The direct contact of the two cell types through integrin αvβ3 on endothelial cells binding L1CAM on CSCs/tumor cells promotes pro-migration signaling in endothelial cells causing increased angiogenesis. This signaling pathway is blocked by cyclic Arg-Gly-Asp-(RGD)-peptide. Bevacizumab, a humanized monoclonal antibody to VEGF, is used routinely in the treatment of patients with recurrent glioblastoma (GBM), renal and metastatic colon and lung cancer. However, little is known regarding bevacizumab effects on cells in the perivascular tumor space. We used established orthotopic xenograft and syngeneic mouse models of GBM to determine entry of bevacizumab into, and uptake by cells in, the perivascular space. We also examined CSCs isolated from GBM for bevacizumab internalization, trafficking and effects on cell survival. In the GBM models, we found that administered bevacizumab entered the perivascular tumor niche and was internalized by CSCs. In the perivascular CSCs, bevacizumab was detected in the recycling compartment or the lysosome, and increased autophagy was found. In CSCs propagated *in vitro*, bevacizumab was internalized rapidly through macropinocytosis with a fraction being trafficked to a recycling compartment and a fraction to lysosomes. We demonstrate that bevacizumab is internalized by CSCs residing in the perivascular tumor niche and macropinocytosis of bevacizumab and trafficking to the lysosome promotes the survival of CSCs, as does the autophagy induced by bevacizumab depletion of VEGF-A. In the workshop, we will discuss the above data, the protocols used to develop the data, how these data fit into our current understanding of anti-angiogenic therapeutics and the development of resistance, as well as the impact on future anti-angiogenic therapy.

Biography

Candece L Gladson has her expertise in the modeling and analysis of angiogenesis and anti-angiogenic therapeutics utilizing both *in vitro* and *in vivo* model systems. Her laboratory focuses on the mechanisms by which the perivascular niche and extracellular environment regulate angiogenesis in vascular tumors; this has included the identification by her laboratory of a cell-cell signaling pathway that modulates angiogenesis and a new mechanism of resistance to anti-angiogenic therapeutics. The overall goal of her laboratory is to develop more efficacious anti-angiogenic therapeutics, aided by the identification of better therapeutic targets.

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