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Mapping Anti-Angiogenic Proteome Associated With Black Raspberry Extract and Gallic Acid in Neuroendocrine Cancer

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BACKGROUND: Angiogenesis is a significant characteristic associated with neuroendocrine tumor (NET) development. Both gallic acid (GA) and black raspberry extract (BRE) have been reported to inhibit angiogenesis and cancer in preclinical models. This study examined the effect of GA and BRE on NET induced angiogenesis using a 3-D fibrin-thrombin clot assay that replicates vessel growth from intact human NETs.

METHODS: Liver NET metastases (N=5) and lymph node NET metastases (N=5) tissue fragments (N=12) were cultured for 14 days in either 1) control media 2) 1mM GA, or 3) 0.5mg/mL BRE. Angiogenesis was quantitated microscopically for angiogenesis initiation and growth after 14days using a previously established index (AI:1-16). Changes within the angiogenesis proteome were determined using a commercially available human angiogenesis array by comparing media levels collected at baseline and 14days. Proteins consistently changed were confirmed using commercially available ELISAs and quantitated in plasma from NET patients and controls.

RESULTS: The percentage of tissue fragments positive for angiogenesis was significantly decreased in response to both GA and BRE. In contrast, in tissues where angiogenesis was observed, reduced growth was only recorded in response to GA. For the fifty-five proteins within the angiogenesis array, four proteins were reduced in response to both GA and BRE.

Modulation of three proteins, platelet factor-4 (PD-4), thrombospondin-2 (THBS2) and chemokine ligand-16 (CXCL16), but not PD-ECGF, were confirmed by ELISA. All four proteins were elevated in patients with NET when compared to controls.

CONCLUSION: BRE and GA inhibits angiogenesis initiation contemporaneous with a modulation within the angiogenesis proteome. This data directs investigation towards targeting PD-4, THBS2 and CXCL16 signaling. Future studies will focus on these pathways to prevent angiogenesis initiation but also identify angiogenic proteome changes linked to vessel growth.

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