Cytokine Profiling Distinguishes Sub Types of Vascular Malformations

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BACKGROUND:
Vascular anomalies is a new, rapidly evolving multidisciplinary field that draws together several surgical and medical specialties. There are two major categories of vascular anomalies: tumors (including hemangiomas, hemangiopericytomas, and other rare vascular neoplasms) and malformations (including capillary, venous (VM), lymphatic (LM), arteriovenous (AVM) and combined forms). Most malformations exhibit endothelial quiescence. For certain patients, however, the disease process is characterized by relentless and continuous progression. The lack of surgical and pharmacological interventions for such cases often results in significant morbidity and death. Numerous studies have demonstrated the dependence of tumor expansion on angiogenesis. Microarray studies have implicated the involvement of other gene families. Circulating angiogenic markers have been identified in the serum and urine of affected patients.
PURPOSE:
The purposes of this study were : A) To evaluate the presence of multiple angiogenic markers in the serum and urine of patients with vascular anomalies using cytokine array analysis and B) to determine whether subsets of malformations could be identified based on cytokine profiling.
METHODS:
Urine was obtained from control children (n=7), and children with the following vascular anomalies: AVM (n=9), Hemangioma (n=9), and VM (n=5). The urine was hybridized to array membranes spotted with cytokine-specific antibodies. Differential cytokine expression patterns were then quantified and subjected to statistical analyses to determine which patterns were significant. Immunohistochemical (IHC) studies were also performed on human AVM tissue to identify cytokine expression and determine patterns of localization.
RESULTS:
Cytokine array analyses of control and patient urines showed the following novel expression patterns: increased expression of Acrp30/Adiponectin in AVM and Hemangioma, increased expression of TIMP-2 (Tissue Inhibitor of Metalloproteinase-2) in Hemangioma, and increased expression of both TRAIL-R3 (TNF Related Apoptosis Inducing Ligand Receptor-3) and uPAR (Urokinase Plaminogen Activator Receptor) in AVM and Hemangioma. IHC revealed areas of local expression of the following proteins in the tissue in and around AVM: KGF/FGF-7, Thrombopoietin, Leptin, Acrp30, TRAIL-R3, and CD54.
CONCLUSION:
Multiple markers of angiogenesis were identified in the urine of patients with vascular anomalies. Cytokine profiling may represent a tool that allows different classes of these anomalies to be distinguished. This study also demonstrated the association of fat-related cytokines in urine of AVM patients. Combining information from previous microarray data concerning the up-regulation of Leptin (among other fat-related genes) with the increased presence of Adiponectin in urine and tissue shown by this work suggests that abnormal tissue adiposity, in addition to angiogenesis, may play a significant role in AVM pathogenesis.