

## **Scavenger Receptor-A Mediates the Endocytosis of the Chaperones gp96(GRP94) and Calreticulin into Antigen Presenting Cells**

**Berwin, B., Post, S.R.<sup>#</sup>, Nicchitta, C.V. and S.V. Pizzo**

Duke University Medical Center, Durham, NC, 27710 and <sup>#</sup>University of Kentucky Medical Center, Lexington, KY, 40536

gp96(GRP94) and calreticulin are endoplasmic reticulum-derived chaperones that function as tumor rejection antigens; immune responses elicited by these proteins result in a suppression of tumor growth and metastasis. Chaperone elicited anti-tumor immune responses are thought to reflect the trafficking of bound peptides into the MHC class-I antigen presentation pathway of professional antigen presenting cells (APC) and through activation of the innate immune system. Here we report that scavenger receptor class-A (SR-A) is the predominant endocytic receptor for gp96 and calreticulin into APC. Ectopic expression of SR-A in HEK-293 cells is sufficient to confer uptake of GRP94 and calreticulin. Calreticulin and gp96 endocytosis is competed by known SR-A ligands, including fucoidin and modified LDL, in macrophages, dendritic cells, and SR-A-expressing HEK cells. These ligands are structurally unrelated, indicating pattern recognition as a determinant in receptor binding. Additionally, macrophages derived from SR-A<sup>-/-</sup> mice are impaired in their ability to bind and internalize gp96 and calreticulin, and SR-A ligands compete for the re-presentation of gp96-complexed peptide antigens. These data identify new roles for SR-A in the regulation of cellular responses to tumor rejection antigens.