

FIZZ1 is a novel macrophage gene in chronic Th2-mediated inflammation

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"Alternatively-activated" macrophages (AAM) are found in Th2-mediated inflammatory settings such as nematode infection and allergic pulmonary inflammation. We have used murine macrophages elicited by nematode infection (NeMac) as a source of in vivo-derived AAM. Using a combination of functional assays and gene expression analysis we have found that NeMacs have a novel IL-4 dependent phenotype characterised by two striking features 1/ the ability to reversibly suppress the proliferation of T cells and 2/ the over representation of FIZZ1 (35% of the subtractive library screening for IL-4 dependent genes; 2% of the total NeMac mRNA), a gene product not previously associated with macrophage function. FIZZ1 is a small, secreted cysteine-rich protein recently identified as an abundantly expressed protein in the broncho-alveolar lavage fluid of a mouse asthmatic model. FIZZ1 has been shown to inhibit the action of nerve growth factor but its function in nematode infection is unknown. We have shown by real-time PCR that FIZZ1 is upregulated in response to infection by the filarial nematodes *Brugia malayi* and *Litomosoides sigmodontis*, and by the gastro-intestinal nematode *Nippostrongylus brasiliensis*, implying a critical role for this gene in the immune response to nematodes. In vitro, FIZZ1 is responsive to both IL-4 and IL-13 and is predominantly expressed in antigen presenting cells activated in Th2 cytokine settings. We have generated an antibody to FIZZ1 and are now correlating RNA expression data with protein expression. We are currently elucidating the role of FIZZ1 in nematode infection through expression analysis in different Th2 mediated inflammatory settings and through functional analysis of recombinant FIZZ1 expressed in both bacterial and mammalian systems.

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