

## **Regulation and Function of Human Immunoglobulin D**

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Immunoglobulin D (IgD) is an enigmatic antibody isotype that mature B cells co-express with IgM through alternative mRNA splicing. We found active T cell-dependent and T cell-independent IgM-to-IgD class switching in B cells from the human upper respiratory mucosa. This process was highly dependent on the activation of B cells by signals from CD40 ligand, B cell-activating factor of the tumor necrosis factor family (BAFF) or a proliferation-inducing ligand (APRIL) and a cytokine combination comprising interleukin-21 (IL-21) and IL-2 or IL-21 and IL-15. IgM-to-IgD class switching required the DNA editing enzyme activation-induced cytidine deaminase and generated local as well as circulating IgD-producing plasmablasts highly reactive to respiratory bacteria. Circulating IgD interacted with a subset of granulocytes, including basophils, in both humans and teleosts through a mechanism involving an IL-4- and IL-3-inducible calcium-mobilizing receptor(s) different from IgG, IgA and IgE receptors. Cross-linking of basophil-bound IgD induced antimicrobial, opsonizing, inflammatory and B cell-stimulating factors including cathelicidin, IL-1, IL-4, IL-13, TNF, and BAFF. By showing dysregulation of IgD class-switched B cells and IgD-armed basophils in autoinflammatory syndromes with elevated IgD and periodic fever such as hyper-IgD syndrome (HIDS), periodic fever-aphtous stomatitis-pharyngitis-adenitis (PFAPA) syndrome, Muckle-Wells syndrome and TNF receptor-associated periodic fever syndrome (TRAPS), our data indicate that IgD orchestrates an ancestral immune surveillance system at the interface between immunity and inflammation.

### **References**

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Immunoglobulin D enhances immune surveillance by activating antimicrobial, inflammatory and B cell-stimulating programs in basophils. *Nature Immunol.* 2009, 10:889-898.

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