**The sulfation of heparan sulfate regulates IL-21 bioavailability and signal strength that control germinal centre B cell selection and differentiation**

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**Abstract**

In antibody responses, mutated germinal centre B ($B_{GC}$) cells are positively selected for re-cycle or differentiation. As the products from GCs, memory B cells and antibody-secreting cells (ASCs) support high-affinity and long-lasting immunity. Positive selection of $B_{GC}$ cells is controlled by signals from B cell receptor (BCR) and follicular helper T ($T_{FH}$) cells-derived signals, in particular the costimulation through CD40. Here we demonstrate that the $T_{FH}$ cell effector cytokine IL-21 joins BCR and CD40 in supporting $B_{GC}$ selection and reveal that strong IL-21 signalling prioritises ASC differentiation *in vivo*. $B_{GC}$ cells, compared to non-$B_{GC}$ cells, show significantly reduced IL-21 binding and attenuated signalling, which is mediated by low cellular heparan sulfate (HS) sulfation. Mechanistically, N-Deacetylase and N-Sulfotransferase-1 (Ndst-1)-mediated N-sulfation of HS in B cells promote IL-21 binding and signal strength. Ndst-1 is downregulated in $B_{GC}$ cells and upregulated in ASC precursors, suggesting a selective desensitisation to IL-21 in $B_{GC}$ cells. Thus, a special biochemical regulation of IL-21 bioavailability and signal strength sets a balance between the stringency and efficiency of GC selection.