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Top Reads

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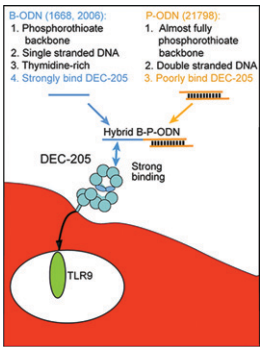
Designing DC Adjuvants



DEC-205 is a cell surface receptor expressed on B cells and type 1 conventional dendritic cells that can bind to a wide range of ligands and facilitate Ag presentation. Previous studies have shown that DEC-205 can bind to synthetic CpG oligodeoxynucleotides (CpG ODN). In this Top Read, Li et al. (p. 1836) observe that DEC-205 most strongly binds with class B ODN, which are single stranded linear ODN with CpG motifs contained in a phosphorothioate backbone. Moderate binding was detected with class C ODN, which also contain a phosphorothioate backbone as well as palindromic sequences that facilitate dimerization. Weak binding was observed with multimeric phosphorothioated class P ODN, and no binding was detected with Class A ODN, which have a phosphodiester backbone. Binding strength correlated with B cell activation and serum IL-12p70 concentrations in mice. In addition, covalent linkage of class B ODN with class P ODN was associated with improved DEC-205 binding and adjuvant activity, as well as enhanced activation of effector $CD8^+$ and resident memory T cells. These findings suggest that CpG ODN can be optimized to improve adjuvant activity and should be explored further in experimental vaccines.

REDD1 Control of Dermatitis

In this Top Read, Mirzoeva et al. (p. 1747) show that the REDD1 gene is an essential immune modulator that influences the initiation of allergic contact dermatitis (ACD). *Redd1*-deficient mice (*Redd1* KO) had normal thymic T cell development. Although *Redd1* KO mice had increased T cells at the ACD site during steady state, there was a profound defect in early T cell migration to the ACD site following challenge. This may be in part due to the diminished expression of chemokines and inflammatory cytokines in the *Redd1* KO mice. Together, these data indicate that REDD1 is a potential target for ACD therapies.

IRF4 Controls B Cell Proliferation

B cell differentiation to Ab-secreting plasma cells is dependent on activation-dependent reprograming of naive B cells and their subsequent cell division. In this Top Read, Patterson et al. (p. 1798) describe IRF4 as a key regulator of B cell growth and proliferation. IRF4-deficient B cells (IRF4cKO) were able to divide in response to stimuli but stalled during subsequent proliferation. RNA-sequencing revealed a failure of IRF4cKO cells to upregulate early genes critical to Ab-secreting cell formation. Indeed, compared with control B cells, IRF4cKO cells failed to upregulate MYC and exhibited reduced mammalian target of rapamycin C1 (mTORC1) activity. MYC overexpression was sufficient to overcome growth defects in IRF4cKO cells, but not the proliferative defect. These data suggest that IRF4 is critical for B cell differentiation through control of growth and maintenance of proliferation.

RNA Virus Reconnaissance

Innate detection of single-stranded RNA viruses is mediated by retinoic acid–inducible gene-I (RIG-I)-like receptors (RLRs), including RIG-I, which is encoded by *Ddx58*, whereas MDA5, encoded by *Ifih1*, can detect dsRNA viruses. Mammalian genomes contain endogenous retroviral elements (ERVs), derived from exogenous retrovirus, and transcripts originating from ERV are detected by RLRs. The epigenetic suppressor KRAP-associated protein (KAP1) is critical to maintaining genomic stability in the presence of ERVs and, in this Top Read, Li et al. (p. 1903) have shown that KAP1 can also directly suppress RLR signaling during RNA virus infection. In keeping with this function, Kap1 deficiency was associated with enhanced antiviral responses. The authors observed that KAP1 promoted repressive histone marks on sites in the *Ddx58* and *Ifih1* promoters, suppressing expression of RIG-I and MDA5. These results define a role for KAP1 in modulating RLR signaling by directly targeting *Ddx58* and *Ifih1*, which, in turn, may allow for the potential immune escape of RNA viruses.

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