Title:

Immunogenomics identifies direct control of NCoR1 on dendritic cell immune tolerance

Abstract:

Dendritic cells (DCs) link innate to adaptive immunity and regulate a fine balance of inflammatory and tolerogenic responses to prevent immune pathology. Conventional Type I DCs (cDC1) cross-present antigens to T cells upon encounter with intracellular pathogens to educate naïve T cells to differentiate into effecter subtypes Th1, Th2 or Tregs. Our overall goal in lab is to understand the transcriptional control of DC responses. It has been reported that strong nuclear receptors (NR) ligands perturb DC responses by changing their activation and cytokine secretion patterns. NRs regulate their target genes by forming complexes with co-repressors like NCoR1. NCoR1 also form complex with other TFs like NFkB and AP-1. We identified that NCoR1 mediated direct repression of immune tolerance in cDCs is essential for development of an optimal immunogenic response. To explore the underlying mechanism we performed integrative genomic analysis of NCoR1 depleted DCs. NCoR1 depletion upregulated a wide-variety of tolerogenic genes in activated DCs, which consequently increased frequency of $CD25^{+}FoxP3^{+}$ regulatory T cells (Tregs) *ex vivo* and *in vivo*. Moreover, NCoR1 strongly represses the PU.1 bound super-enhancers on major tolerogenic genes upon activation. NCoR1 depletion reduced RelA activity after activation whereas RelB activity was unaffected providing DCs a tolerogenic advantage. Interestingly, our genomic data showed an enriched anti-viral network as well in activated NCoR1 KD DCs. These DCs secrete high IFNβ1 and inhibit viral infection by generating a cascade of anti-viral responses against negative strand RNA viruses like Sendai, VSV and NDV. We validated the findings *ex vivo* and *in vivo* using control and $NCoR1^{DC-/-}$ animals. NCoR1 has been reported to form complexes with diverse HDACs to repress their target genes. Therefore we speculated that differential HDAC complex with NCoR1 might be controlling these dichotomous antiviral *vs* tolerogenic responses. Here we will discuss further how we identified the mechanisms underlying the transcriptional control of these diverse responses by NCoR1 in DCs.