



Category: Miscellaneous

NCoR1 is a master repressor of the tolerogenic program in dendritic cells

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Abstract

The therapeutic potential of tolerogenic dendritic cells (DCs) for autoimmune disorders and transplantation has been widely proposed. We show here for the first time that nuclear receptor co-repressor 1 (NCoR1) strongly represses the tolerogenic program in activated DCs despite of its known immunogenic role in macrophages that intriguing the paradigm of immune regulation in this lineage through NCoR1. DC specific conditional NCoR1 knock out (NCoR1DC^{-/-}) mice also shows tolerogenic behavior as we found in our cell line NCoR1 KD CD8 α ⁺ DCs and consequently increase in Treg cells *in-vivo* or *in-vitro*. Bacterial and parasitic infection in NCoR1DC^{-/-} animals enhanced Treg development with a concomitant increase in disease burden. Likewise, adoptive transfer of activated NCoR1 KD DCs in helminth-infected mice increased both Tregs and intestinal worm load which suggest NCoR1 as a direct switch controlling tolerogenic genes in DCs. Next we employed integrative genomics approach to dissect the tolerogenic mechanism of NCoR1 in CD8 α ⁺ DCs in which we found globally NCoR1 prevent most of the tolerogenic genes from recruiting activating transcription factor RelA which allows these cells to mount pathogen specific immune responses. Interestingly we also found most of these tolerogenic genes were marked by super enhancers which might be super repressed by NCoR1 suggesting NCoR1 as a global corepressor for tolerogenic program in DCs and highlight novel mechanism of tolerogenicity in DCs via NCoR1 which can be flourished in different autoimmune disease pathogenesis.

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