Title: **Analogs of thalidomide act as immunomodulators of human dendritic cells.**

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Abstract:

Dendritic cells (DCs) are pivotal in orchestrating both innate and acquire immunity through cytokine-mediated fashions. Series of recent analyses have revealed that DCs also play a pathogenic role in inflammatory conditions such as allergy and autoimmune diseases by their dysregulated function and cytokine production. According to the function of novel anti-tumor drugs, so-called Immunomodulatory Drugs (IMiDs) that have the potential to enhance T and NK cells function and to induce selective reduction of regulatory T cells, we hypothesized that these agents could have the potential to modulate the functions of DCs as the center of the immunoregulatory system. However, the precise mechanisms underlying their anti-tumor effects still largely remain unclear. Here we investigated the effect of two cognate immunomodulatory analogs of thalidomide, lenalidomide (LEN) and pomalidomide (POM) on the function of human myeloid DCs (mDCs), blood $CD11c^+$ DCs and monocyte-derived DCs. We found that both reagents at clinical concentration of 0.1 μM to 1 μM did not affect cell survival and CD86 expression in response to LPS or R848. Either LEN or POM inhibited dose-dependently the production of IL-12 and TNFα. Both LEN and POM significantly enhanced the production of IL-10 from mDCs in response to the TLR ligands, and this capacity of POM was stronger than that of LEN. It has been shown that LEN binds to and inactivate E3 ubiquitin ligase Cereblon to

downregulate IRF4 in myeloma cells. In mDCs, we also found that both LEN and POM downregulated IRF4 but upregulated IRF8 mRNA, which can mediate Th1-related response in human DCs. Our data suggest IMiDs, although enhance the effector cell function, lead to tolerogenic action at DC phase. This result provides novel insights into immunomodulatory function of LEN and POM.