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Regulation of dendritic cell differentiation, maturation and activation

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ABSTRACT

The human immune system efficiently protects the host from exogenous pathogens such as bacteria, virus and parasites and endogenous threats such as damaged cells and tumors. Invasion of pathogens and other threats activate the innate immunity causing secretion of pro-inflammatory cytokines with the subsequent antigen presentation and activation of the adaptive immunity resulting in T and B cell responses. The professional antigen presenting cell (APC), the dendritic cell (DC), is crucial for connecting the innate and adaptive immune system. DCs have a critical role for activating efficient immune responses, and they are key targets for negative regulatory mechanisms that ensure adequate inflammatory responses. In addition, based on their unique capacity, DCs have been used in many immunotherapy trials since DC based vaccines have demonstrated an ability to induce anti tumoral immunity. However, many aspects of DC biology are still unexplored, especially the regulation of DC differentiation, maturation and activation.

The aim of this thesis was to investigate the regulating mechanisms of novel regulators and conventional chemotherapeutic drugs and their effect on the differentiation, maturation and activation of DCs.

Initially, we investigated the gene expression of suppressor of cytokine signaling (SOCS) members and their regulating role in LPS induced DC maturation. We showed that SOCS2, SOCS3 and SOCS6 are significantly induced after LPS treatment, and that SOCS2 influences the maturation of human monocyte-derived DC (moDC). Furthermore, we demonstrated that various toll-like receptor (TLR) ligands induce SOCS2 gene expression in human DCs, and that TLR4 signaling regulates SOCS2 transcription in an autocrine/paracrine type I IFN loop via STAT3 and STAT5. Using SOCS2 deficient mouse, we revealed that although SOCS2 does not regulate murine lymphoid DC differentiation *in vivo*, SOCS2 is necessary for the differentiation of GM-CSF and IL-4 induced DCs *in vitro*, likely by regulating GM-CSF signaling. Similar to human DCs, SOCS2 also affects LPS induced mouse DC maturation, and thereby regulates the antigen presenting ability of DCs with consequences for activation of CD4⁺ T cell. In this thesis, we also investigated the effect of conventional chemotherapeutic drugs on human DCs. We demonstrated that Dexamethasone, Doxorubicin, Cisplatin and Irinotecan inhibit the differentiation of human moDC to various extents. However, Cisplatin treatment of human DCs leads to increased T cell activation, a potentially beneficial effect of Cisplatin mediated by the increased expression of IFN- β cytokine.

In conclusion, we have demonstrated that SOCS2 positively regulates the differentiation, maturation and antigen presenting ability of DCs. Furthermore, TLR4 signaling regulate SOCS2 transcription in an autocrine/paracrine type I IFN loop. The differentiation of human moDC may be negatively influenced by Cisplatin, but treatment of human DCs may cause increased T cell activation, a finding deserving clinical exploration.