A paradoxical role for Flt3 ligand in tumor immune response reveals homeostatic control of NK and Treg cells by dendritic cells

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Flt3 ligand (FL) induces differentiation and proliferation of classical dendritic cells (cDCs) and is a promising molecule in therapies of cancer and vaccination, but has mixed effects in clinical trials. To better understand the role of FL/DCs axis in cancer, we monitored tumor growth in a mouse model of melanoma in the context of low, normal or high levels of FL. Paradoxically, both FL depletion and overexpression stalled tumor growth and increased animal survival as compared to control. By following kinetics of recruitment of dendritic and lymphocyte populations in FL-low context, we showed that FL deficiency led to a profound decrease of cDCs subsets and inhibition of Tregs proliferation and recruitment in draining lymph nodes (dLNs) and tumor microenvironment. These changes did not affect drastically migratory DCs (mDCs), and were accompanied by higher frequency of helper T cells and activated T lymphocytes, but NK cells frequency remained low, indicating that in FL-deficient mice tumor growth is predominantly controlled by the adaptive immune system. In contrast, FL overexpression led to a massive recruitment of activated NK cells in the dLNs and into the tumor, suggesting that the high FL levels favor the innate anti-tumor response, despite the presence of cDCs and Tregs. NK cell depletion abrogated the beneficial effect in this setting. Further analysis in mice determined that neither NK recruitment, nor NK precursor differentiation depend on FL levels. Instead, using genetic model of inducible DC-depletion under the control of zDC transcription factor specific for cDCs, we showed unambiguously that, in vivo, NK homeostasis is controlled by FL-dependent cDCs. Thus, FL-dependent DCs control the balance between tumor tolerance and rejection by regulating Treg and NK cells homeostasis. In support of the role of FL in human cancer, analysis of human gene expression data confirmed the paradoxical effect of FL as well as FLT3 and zDC/ZBTB46 expression levels on survival in several types of cancer.
As a proof-of-principle, we showed that the combination of FL overexpression and Tregs depletion resulted in regression of established tumors and dramatically improved survival of tumor-bearing mice.

Keywords : dendritic cells, Tregs, Natural killer cells, FLT3-L, Cancer, Human, Mice
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