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Universiteit Leiden



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Title: Innate immune responses of natural killer cells and macrophages against bone sarcomas : towards cellular immunotherapy

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Propositions

pertinent to the thesis

Innate Immune Responses of Natural Killer cells and Macrophages against Bone Sarcomas

1. Anti-EGFR therapeutic antibody cetuximab can potentiate and more specifically direct the cytotoxic activity of NK cells toward osteosarcoma and Ewing sarcoma cells. (This thesis)
2. Prolonged interactions between sarcoma cells and tumor-infiltrating NK cells may compromise NK cell cytotoxic activity and facilitate tumor cell escape. (This thesis)
3. Activating NK cells with interleukin-15 before tumor cell encounter and/or triggering of antibody-dependent cytotoxicity may prevent inhibition of the cytolytic activity of NK cells by sarcoma cells. (This thesis)
4. Macrophages, whose presence in osteosarcoma tumors is supportive for patient prognosis, may be harnessed for direct anti-tumor responses by activation with bacterial derivatives like L-MTP-PE in the presence of interferon- γ , or by tumor-reactive therapeutic antibodies like cetuximab. (This thesis)
5. CD70 could serve as a tumor cell-specific target for immunotherapies, since CD70 is very restricted in healthy tissues but present in certain osteosarcoma specimens. (This thesis)
6. “Oncolytic viruses may represent a unique strategy for combining tumor debulking activity (via direct tumor lysis and/or vascular attack) with potent activation of adaptive and innate immune responses.” (Russel, *Nat. Biotechnol.* 2012, 30:666)
7. “Tumor-promoting inflammation and protective tumor immunity are dynamically interconnected processes that vie for dominance as tumor cells develop and transit through cancer immunoediting.” (Schreiber, *Science* 2011, 331:1568)
8. Since “thus far [...] adoptive transfer of NK cells, either autologous or allogeneic, has been largely unsuccessful for treating patients with solid tumors” (Parkurst, *Clin. Cancer Res.* 2011, 17:6296), future research should assess how the inhibitory character of the cancer microenvironment can be modified; how the cytolytic activity of the NK cells can be optimally induced and preserved *in vivo*; and how the infiltration of the NK cells into solid tumors can be enhanced.
9. “Parallel mechanisms of signal integration through activating receptors, co-stimulatory receptors and cytokine receptors [may] facilitate a productive effector response in both NK cells and T cells” (Sun, *Nat. Rev. Immunol.* 2011, 11:652).

10. Usage of non-standard abbreviations can complicate readability, understanding and pronunciation, but sometimes their confusion opens up new perspectives for fruitful research lines.
11. The content of long German sentences is not necessarily greater than that of shorter English and somewhat shorter Dutch sentences; however, it can be easier to conceal little content within lengthy German phrases.
12. Just as a German may miss the quality of German bread in the Netherlands, a Dutchman may miss the quality of Dutch bike paths in Germany.

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