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Effective immunotherapy of large established tumors with CpG oligonucleotides and dendritic cells in murine tumor models

Rall K., Heckelsmiller K., Schlamp A., Endres S. and Hartmann G.

To test the therapeutic potential of dendritic cells (DC) and oligonucleotides containing immunostimulatory CpG motifs (CpG ODN) tumors were induced by s.c. injection of syngeneic C26 or Renca tumor cells in Balb/c mice. In a first protocol DC were coincubated with irradiated tumor cells and activated by CpG ODN 1826 in vitro. Injection of these DC on day 5 after tumor challenge induced a tumor-specific immune response which cured mice. In this protocol no CpG ODN was present in vivo. In a second protocol weekly injections of CpG ODN without DC into the margin of the tumor were performed. This monotherapy lead to rejection of local and distant established tumors as a result of the combined activation of innate effectors and tumor specific CD4 and CD8 T cells. In a third approach we combined both protocols. CpG ODN were coinjected with antigen-loaded DC in mice with large established tumors. In this setting the effect of DC alone was poor. Coinjection of CpG ODN potently improved efficacy of DC. The optimal regimen was found to be coinjection of DC and CpG at sites distant of the tumor and simultaneous injection of CpG ODN into the tumor margin. This therapy controlled tumor growth of tumors with 1.4 cm in diameter. In conclusion we established an optimized protocol based on a combination of DC and CpG ODN which allows the control of large established tumors. These results form the basis for clinical studies testing DC and CpG ODN for the treatment of human cancer.

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