

Combining Toll-like receptor agonists and immune costimulation for cancer therapy

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To stimulate a coordinated immune response against cancer, we have combined administration of the Toll-like receptor (TLR) agonist, CpG, with an agonistic antibody providing T cell costimulation through 4-1BB (CD137) in mouse tumor models. This combination was demonstrated to induce eradication of a large proportion of established subcutaneous tumors of a variety of histological types. Intratumoral administration was more effective than systemic delivery, and was also able to induce regression of contralateral tumors. CD8⁺ T cells were necessary for tumor eradication, and there was a requirement for NK cells for optimal anti-tumor activity. Both type I and type II interferons also played a crucial role and the TLR adaptor molecule MyD88 was necessary for effective therapy. Intratumoral injection of CpG led to activation of dendritic cells and dramatic changes in the expression of many chemokines and inflammatory mediators. In addition, greater proportions of activated T cells were present in the circulation of treated mice. Interestingly, immunological memory was induced leading to resistance to tumor rechallenge, and B cells were required for the establishment of this memory response. This combination of immunomodulators led to activation of both innate and adaptive immune components resulting in effective cancer therapy.