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Triple Immunotherapy to Overcome Immune Evasion by Tumors in a Melanoma Mouse Model

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Abstract : Introduction: Current evidence confirms that both innate and adaptive immune systems are capable of recognizing and abolishing malignant cells. The emergence of cancerous tumors in patients is, therefore, an indication that certain cancer cells can resist elimination by the immune system through a process known as “immune evasion”. In fact, cancer cells often exploit regulatory mechanisms to escape immunity. Such mechanisms normally exist to control the immune responses and prohibit exaggerated or autoimmune reactions. Recently, immunotherapies have shown promising yet limited results. Therefore this study investigates several immunotherapeutic combinations and devises a triple immunotherapy which harnesses the innate and acquired immune responses towards the annihilation of malignant cells through overcoming their ability of immune evasion, consequently hampering malignant progression and eliminating established tumors. The aims of the study are to rule out acute/chronic toxic effects of the proposed treatment combinations, to assess the effect of these combinations on tumor growth and survival rates, and to investigate potential mechanisms underlying the phenotypic results through analyzing serum levels of anti-tumor cytokines, angiogenic factors and tumor progression indicator, and the tumor-infiltrating immune-cells populations. Methodology: For toxicity analysis, cancer-free C57BL/6 mice are randomized into 9 groups: Group 1 untreated, group 2 treated with sterile saline (solvent of used treatments), group 3 treated with Monophosphoryl-lipid-A, group 4 with anti-CTLA4-antibodies, group 5 with 1-Methyl-Tryptophan (Indolamine-Dioxygenase-1 inhibitor), group 6 with both MPLA and anti-CTLA4-antibodies, group 7 with both MPLA and 1-MT, group 8 with both anti-CTLA4-antibodies and 1-MT, and group 9 with all three: MPLA, anti-CTLA4-antibodies and 1-MT. Mice are monitored throughout the treatment period and for three following months. At that point, histological sections from their main organs are assessed. For tumor progression and survival analysis, a murine melanoma model is generated by injecting analogous mice with B16F10 melanoma cells. These mice are segregated into the listed nine groups. Their tumor size and survival are monitored. For a depiction of underlying mechanisms, melanoma-bearing mice from each group are sacrificed at several time-points. Sera are tested to assess the levels of Interleukin-12 (IL-12), Vascular-Endothelial-Growth Factor (VEGF), and S100B. Furthermore, tumors are excised for analysis of infiltrated immune cell populations including T-cells, macrophages, natural killer cells and immune-regulatory cells. Results: Toxicity analysis shows that all treated groups present no signs of neither acute nor chronic toxicity. Their appearance and weights were comparable to those of control groups throughout the treatment period and for the following 3 months. Moreover, histological sections from their hearts, kidneys, lungs, and livers were normal. Work is ongoing for completion of the remaining study aims. Conclusion: Toxicity was the major concern for the success of the proposed comprehensive combinational therapy. Data generated so far ruled out any acute or chronic toxic effects. Consequently, ongoing work is quite promising and may significantly contribute to the development of more effective immunotherapeutic strategies for the treatment of cancer patients.

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