THERAPEUTIC EFFECT OF PD-1 BLOCKADE IN THE MBT-2 MURINE BLADDER CANCER MODEL.

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Background: Non-specific immunotherapy using Bacillus Calmette-Guerin (BCG) is currently the preferred treatment to prevent non-muscle-invasive bladder cancer (NMIBC) recurrence after surgery. However, it remains suboptimal as recurrences and progressions are respectively observed in 60% and 20% of cases. Among the most promising alternative approaches to BCG is the blockade of immune checkpoints. Using the MBT-2 murine bladder cancer model, we analyzed the phenotype of the tumor-infiltrating immune cells, and their expression of various immune checkpoints such as PD-1, CTLA-4, LAG-3, and TIM-3. We hypothesized that blocking PD-1/PD-L1 pathway would boost the anti-tumor response.

Methods: MBT-2 tumors were grown subcutaneously in CH3 mice. After tumor dissociation using a GentleMACS, tumor-infiltrating immune cells and their immune checkpoint expression was characterized by multicolor flow cytometry. PD1 blockade was performed by 4 i.p. injections of anti-PD-1 monoclonal antibody (mAb) in MBT-2-tumor-bearing mice.

Results: The analysis of MBT-2 tumors showed that their microenvironment is characterized by the presence of cells with a suppressor phenotype. Indeed, regulatory T cells (Treg) (CD3ε+CD4+FOxP3+) represented ≈23% of the CD4+ tumor-infiltrating-lymphocytes (TILs) (CD3ε+CD4+) and about 29% of these TILs were Tr1 (CD3ε+CD4+IL10+). Moreover, the majority CD4+ and CD8α+ TILs expressed PD-1 and TIM-3 but very few or no CTLA-4 or LAG-3 molecules. PD-1 pathway blockade in mice bearing MBT-2 tumors resulted in a drastic reduction of tumor growth and even the cure of 1 out of 6 mice.

Conclusions: These data indicate that in MBT-2 tumors, blocking the PD1/PD-L1 pathway could stimulate an effective anti-tumor immune response. This protection might be improved by combining PD1/PD-L1 blockade with the blockade of other immune checkpoint such as TIM-3 which is also highly express on MBT-2 tumor TILs. Finally, these results also suggest that combination of immune checkpoint inhibition with BCG therapy might result in an even more effective therapy against NMIBC.

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