Rethinking Cancer Immunotherapies

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Background

Immune checkpoint pathways are the signaling pathways which regulate the immune response to minimize the peripheral tissue damage during an immune response. These immune checkpoint signaling pathways are activated by receptor-ligand mediated interactions. As seen in the formation of many kinds of tumors, the improper regulation of the immune checkpoint receptors and/or ligands in the tumor microenvironment lead to a suppressed immune response against the tumor. Cytotoxic T lymphocyte associated antigen 4 (CTLA4) or CD 152 is an immune checkpoint receptor expressed on T lymphocytes. When engaged with its ligands, which also happen to be the ligands for the T cell Co-stimulatory Receptor, CTLA4 inhibits T cell activation. Experimental data suggests that CTLA4 is overexpressed in the tumor microenvironment leading to a suppressed immune response against the tumor. Ipilimumab, a fully humanized monoclonal antibody for CTLA4 was developed and rigorously tested in the clinic. In 2010, Ipilimumab was US FDA approved for the treatment of patients suffering from advanced and unresectable metastatic melanoma as it was the first ever drug to show a survival benefit in advanced metastatic melanoma. Even though treatment with Ipilimumab showed a survival benefit, the response rates were not satisfactorily high. The response was also delayed and in few patients the response was seen after an initial increase in the tumor burden. In this poster we suggest the administration of different therapeutic agents in synergy with Ipilimumab, also known as combination therapies, for a faster and more efficient response. The delayed response might be explained due to an insufficient immune response which might happen due to the following three possibilities:

(i) Insufficient amounts of antigen available.
(ii) The increase in T cell activation due to the blockade of CTLA4 might not be sufficient.
(iii) The effector T cell functioning might be reduced.

We put forward a few combination therapies with Ipilimumab that can overcome the above three possibilities and hopefully increase the response rates as well as time for response in the treatment of advanced metastatic melanoma.