Search for receptors in immune cells that bind cancer cell antigens and their activation in silent cases

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Abstract

The immune checkpoint plays an important role in keeping immune cells in check for protecting tissues and organs from attack by the body's own immune system. Similar concepts also apply in how cancer cells managed to fool immune cells through the surface display of particular antigens that mimic those exhibited by normal body cells. Specifically, cancer cells display antigens that bind to receptors on immune cells that subsequently prevent an attack on the cancer cells. Such binding between cancer antigens and immune cell receptors can be prevented through the use of checkpoint inhibitors antibodies specific for particular receptors on immune cells; thereby, unleashing immune cells to mount an immune response against cancer cells. While demonstrating good remissions in many patients where tumours shrunk substantially after administration of checkpoint inhibitors, cases exist where an overactivated immune system cause harm to organs and tissues culminating in multiple organ failure. Analysis of such toxicity effects of checkpoint inhibitors revealed that generic nature of targeted immune receptor plays a pivotal role in determining extent of side effects. Specifically, if the target immune receptor participates in checkpoints that prevent immune cells from attacking host cells, unleashing such receptors in cancer therapy may have untoward effects on patient's health. Hence, the goal should be the selection of immune cell receptor specific to cancer cell antigens and which does not bind antigens or ligands displayed by the body's cells. Such receptors would provide ideal targets for the development of checkpoint inhibitor antibodies for unleashing immune cells against cancer cells. To search for non-generic receptors that bind cancer cell antigens only, a combined computational and experimental approach could be used where ensemble of surface antigens on cancer cells and available receptors on immune cells could be profiled by biochemical assays. Downstream purification of ligands and receptors would provide for both structural elucidation and amino acid sequencing useful for bioinformatic search of homologous sequences. Knowledge of the antigens' and receptors' structures and amino acid sequence would subsequently serve as inputs to computational algorithms that models molecular docking events between receptor and antigen. This paves the way for heterologous expression of putative ligand and receptor in cell lines cultured in co-culture format for assessing binding between ligand and receptor, and more importantly, its physiological effects. Ability of immune receptor to bind to ligands on normal cells could also be assessed. Similar co-culture studies could be conducted with cancer cells and different immune cell types to check for reproducibility of observed effect in cell lines. Finally, antibodies could be raised for candidate receptors whose inhibition would not result in systemic attack of immune cells on host cells.

Keywords: checkpoint inhibitor, immunotherapy, antibodies, ligands, antigens, receptors, cancer cell, immune cells, structural studies, receptor-antigen binding,

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