Targeting Mismatch Repair Makes Cancer Visible to the Immune System.

To grow and become metastatic, tumours must find ways to evade several layers of controls which are in place in our body. The immune system, a complex network of cells and antibodies has been designed by evolution to protect us not only against virus and bacterial infections, but also cancer. To escape, tumours continuously evolve, altering the mechanism that makes them detectable or blocking the activity of specific effector cells of the immune system (cytotoxic T cells). Any therapeutic approach, which aims to spark cancer immunity, is therefore potentially relevant for increasing the survival rate of cancer patients; this is particularly true for immune-checkpoint modulators, whereby specific antibodies are administered to tackle cancer-mediated T cell blockade and restoring the immune control.

Recent findings obtained by Giovanni Germano a postdoc in the laboratory of Prof. Bardelli at the University of Torino and Candiolo Cancer Institute has put forward an innovative approach. They have tested the hypothesis that inactivation of the mechanism that corrects the “user manual” of our cells (the DNA, namely a long sequence of Adenine, Guanine, Thymine and Cytosine that code our life) could be used to make cancer more prone to immune surveillance. Notably, as a result of inactivating the mechanism to repair incorrect pairing of bases during DNA replication, tumours acquire a new repertoire of alterations, which are called neoantigens. In particular, single nucleotide variant (change in a single base) and insertion/deletion of one or more nucleotides may alter the identity of the protein that is detected as ‘non self’, and considered as a potential pathogen by the immune system. Most notably these kinds of alterations, associated with DNA mismatch repair machinery (MMR), are present in approximately 15 % of all colorectal cancer patients, the so called microsatellite instable sub-group (MSI). Microsatellites are specific region of the DNA where Cytosine and Adenine (CA) are repeated n times. When the expansion or deletion of these portions alters the number of CA repetition, owing to MMR alterations, the regions are defined ”instable”. Interestingly the MSI tumors have a peculiar phenotype and the alterations in the MMR machinery promote tumor initiation and growth; however, they are associated with favorable prognosis. It has recently been shown that immune checkpoint blockade is more efficacious in patients with MSI status than in patients with microsatellite stable (MSS) tumors. Bardelli and Germano started this project based on the striking results obtained by immune therapies in mismatch repair deficient tumours, and wondered whether we could develop preclinical models that would to help better us understand the mechanistic bases of those unprecedented results observed in the clinics.

To elucidate the role of MMR in tumorigenesis and in the response to immunotherapy, Germano and colleagues targeted Mlh1 (a component of the MMR machinery altered in 85% of MSI patients) in murine breast, colon cancer, and pancreatic ductal adenocarcinoma cells to generate isogenic sets of MMR-proficient and MMR-deficient cell lines (cells that differ only for the presence/absence of Mlh1). While both cells grew at similar rates and rapidly formed tumors in mice without a functional immune system (immune-compromised mice), only MMR-proficient cells formed tumors in immune-competent mice. Consistent with these findings, we depleted cytotoxic T cells from mice obtaining that MMR-deficient cells formed tumors and supporting the hypothesis of a role of T cells in the immune control. The analysis of the DNA revealed that the number of the alterations (mutational load), the number of neoantigens, and T-cell receptor diversity (receptor present on T cell surface that contributes to T cells activation in response to neoantigens) increased over time in MMR-deficient, but not in MMR-proficient, cells.

Overall these findings show that MMR deficiency induces neoantigen production to promote durable immune surveillance and suggest that inactivation of DNA repair may enhance the immunogenicity of tumors defined “cold” for the low immune attractive appeal.

We were very excited when we observed for the first time that evoking dynamic neoantigen profiles triggered immune- surveillance in mice studies. In light of our findings, we believe blocking mismatch repair is an attractive therapeutic target mechanism. Our approach established a simple, yet paradoxical, principle: inhibition of the body’s DNA damage mismatch repair machinery can be exploited to continuously stimulate the creation of new cancer antigens in tumours. Overall, these data indicate a potential way for converting immune-cold refractory patients, into sensitive cases immune hot tumors.