IJAE
Vol. 123, n. 1 (Supplement): 102, 2018
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

The impact of T cell mediated immune surveillance on epithelial cancer cells with mismatch repair alterations

Giovanni Germano[1], Simona Lamba[2], Giuseppe Rospo[2], Alessandro Magrì[2], Silvia Marsoni[3], Maurizio D'Incalci[4], Enrico Giraudo[5], Federica Di Nicolantonio[1] and Alberto Bardelli[1]

[1] Candiolo Cancer Institute, Dipartimento di Oncologia, Università degli Studi di Torino, Candiolo, Italia
[2] Candiolo Cancer Institute, FPO, IRCCS, Candiolo, Italia
[3] IFOM - The FIRC Institute of Molecular Oncology, Precision Oncology, Milan, Italia
[4] IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Head, Department of Oncology, Milan, Italia
[5] Candiolo Cancer Institute – FPO, IRCCS,, Laboratory of Transgenic Mouse Models, Candiolo, Italia

The impact of T cell mediated immune surveillance on epithelial cancer cells with mismatch repair the conflicting models of colorectal Lynch syndrome pathogenesis—MMR deficiency as a late event 3,8,53 versus MMR deficiency as an early event 17,19,20 —can only be reconciled by a unifying model tha t accepts the existence of distinct pathways of colorectal carcinogenesis in Lynch syn- drome (Fig. 5). Indeed, our study provides histological and molecular evidence that Lynch syndrome-associated colorectal cancers do not follow one single pathway, but three path- ways separated from each other by the type and timing of key mutation events: colorectal cancers in Lynch syndrome can in fact grow out from MMR-profici ent adenomas after secondary inactivation of the MMR system the conflicting models of colorectal Lynch syndrome pathogenesis—MMR deficiency as a late event 3,8,53 versus MMR deficiency as an early event 17,19,20 —can only be reconciled by a unifying model tha t accepts the existence of distinct pathways of colorectal carcinogenesis in Lynch syn- drome (Fig. 5). Indeed, our study provides histological and molecular evidence that Lynch syndrome-associated colorectal cancers do not follow one single pathway, but three pathways separated from each other by the type and timing of key mutation events: colorectal cancers in Lynch syndrome can in fact grow out from MMR-profici ent adenomas after secondary inactivation of the MMR system Mismatch repair (MMR) is a DNA repair mechanism that ensures the fidelity of DNA replication. In highly proliferative organs the MMR mechanism is relevant for maintaining the correct genetic information. In the colon, the bottom of each crypt, 4-6 stem cells contribute to the enormous amount of colonocytes and host the potential of accumulating genetic and epigenetic changes. Mismatch Repair alterations are considered early event in the transition from colonocytes to adenoma and some colorectal cancer developed from MMR-deficient precursor lesions. Interestingly, recent evidences demonstrate that a subset of patients with alterations in MMR respond prominently to immune checkpoint blockade leading to the hypothesis that the presence of high number of somatic mutations may be responsible for effective recruitment of immune-cells and consequently of surveillance. To prove the hypothesis, we genetically inactivated a component of MMR machinery, MutL homolog 1 (MLH1), in murine colorectal cancer cells. MMR inactivation increased the mutational burden and led to dynamic mutational profiles, resulting in persistent renewal of neoantigens over time. The histological analyses of tissues didn't reveal differences in size and morphology of CT26 colorectal cancer cell lines. Interestingly, isogenic MMR deficient cancer cells were unable to form tumors when injected subcutaneously or orthotopically in syngeneic mouse models according to cell-passage number. To distil the role of the immune system, we injected MMR deficient cells in the presence of depleting CD8 antibody whereas isotype matched antibodies served as controls. Interestingly, MMR deficient cells readily formed tumors in syngeneic mice only when CD8 T cells were suppressed. To test the effects of DNA repair inactivation also on fully established tumors we implanted a fragment of MLH1 KO tumour in syngeneic mouse models. The immunological repertoire of MLH1 KO tumours revealed an increased level of CD45+ cells and activation of cytotoxic CD8+ T cells by IFNγ suggesting that functionally reactive T cells might be responsible for the impaired tumorigenesis of MMR deficient cells. To test the activation of T cells, IFNγ and CD8+ cells were stained by immunofluorescence in control and Mlh1 KO clones. These results led us hypothesize that enforced increase of the number of mutations in cancer cells could foster T cell infiltration restricting cancer growth and this might be beneficial for therapeutic purposes.