Inflammation, immunity and cancer

A central role in the pathogenesis and progression of cancer is attributed to our immune system, both in the innate and adaptive component. It is also known that immunity can contribute to the initiation and progression of cancer, but also to limit its onset and expansion. This line of research is dedicated to understanding the molecular mechanisms that immunity uses in cancer. One line of research concerns the role of proinflammatory cytokines in tumors, and uses it as a model system in thyroid cancer. We have shown that interleukin 8 (IL8), secreted both in an autocrine and paracrine way in this tumor, enhances the invasive capacities and the stemness of the tumor cells. IL8 also induces in these cells the expression of immune checkpoints PD-L1 / 2 and PD-1, molecules capable of suppressing antitumor immunity. The expression of PD-1 and its ligands on the tumor cell creates an autocrine circuit with protumorigenic effects. This circuit activates the MAPK pathway in a SHP2/RAS/RAF-dependent manner. We have shown that inhibition of this circuit with nivolumab reduces the proliferation, motility and tumorigenesis of tumor cells. We are also studying the effect of PD-1 inhibition in combination with other drugs on cancer cells by evaluating immunogenic cell death, as well as the effect of such combinations on the inflammatory immune component of such tumors. Another line of research investigates the role of innate immunity receptors, such as formyl peptide (FPR) and Toll like (TLR) receptors, in the modulation of cancer-associated inflammation. We have shown that FPR1 activates the inflammatory resolution pathway in gastric carcinoma (GC) cells. Inflammation is in fact actively suppressed by specialized lipid mediators (SPMs), synthesized starting from polyunsaturated fatty acids (PUFA) omega 3/6 by cyclooxygenase (COX2) and lipoxygenase (ALOX5 / 15) enzymes. Activation of FPR1 induces an increase in enzymes, SPMs and respective receptors, causing a significant reduction in inflammation and angiogenesis. Indeed, a diet rich in PUFA increases plasma SPM levels and significantly reduces the growth of GC cell xenografts in the mouse model, by reducing angiogenesis. Similar studies have shown that TLR7 controls the resolution of inflammation and tumor angiogenesis in lung cancer (NSCLC). In cases of GC hypomorphic alleles of FPR1 correlate with disease predisposition; in NSCLC TLR7 mRNA levels correlate directly with ALOX15 and inversely with angiogenesis. These studies open up new diagnostic and therapeutic perspectives in cancers typically associated with inflammation.

Neoplasms with defects in DNA repair by homologous recombination, such as carcinomas with BRCA1 / 2 mutations, show sensitivity to poly (adenosine diphosphate [ADP]) ribose polymerase (PARP) inhibitors. These, by amplifying the damage to the DNA, cause an increase in the "mutational burden" with an increase in the expression of PD-L1. To identify tumors that bind to the treatment with PARP inhibitors, it is necessary to identify new biomarkers capable of detecting DNA repair defects by homologous recombination. Recently, in preclinical studies we have reported that CCDC6 deficient cells behave like BRCA defective cells, exhibiting sensitivity to PARP1 / 2 inhibitors. CCDC6 is a tumor suppressor that controls DNA damage response and genome stability in primary cancers. Low levels of CCDC6 correlate with homologous recombination defect in tumors of the pomon, colon, prostate, and bladder. In such neoplasms, the use of PARP inhibitors in association with DNA methyltransferase (DNMTi) inhibitors increase the cytotoxic effects of PARPi by increasing the trapping of PARP1 to DNA. The accumulation of DNA damage results in a high mutational burden of the tumor with exposure of tumor neoantigens, and an increase in the T-type lymphocyte infiltrate in the tumor microenvironment. These events determine a compensatory increase in the PD-PD-L1 complex with the possibility of using inhibitors of immune checkpoints.

References:


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