Tryptophan 2,3-dioxygenase inhibition: a possible target in cancer immunotherapy

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Recent studies suggest that TRP degradation is a mechanism employed by a broad range of tumor to suppress immune response. Tryptophan 2,3-dioxygenase (TDO), previously believed to be a liver- and neuron-specific enzyme, catalyzes the first and rate limiting step of TRP oxidation yielding kynurenine (KYN). Many studies propose an alternative route of TRP degradation in tumor via TDO. T lymphocytes sense low levels of TRP, block their proliferation and differentiate into Treg, leading to immunosuppressive microenvironment. Pharmacologic inhibition with the selective TDO inhibitor 680C91 increased cellular sensitivity to anoikis, and reduced TNBC proliferation, migration, and invasion in a breast cancer cell line. TDO inhibition may represent an additional compelling target for cancer immunotherapy. This project aims to extend the knowledge in TDO role on immune function and tumor biology, by studying the expression and function of TDO on human DCs and cancer cell lines. TDO has been found in in human solid tumors and in some cancer cell lines, however its inhibition on latter function, in vitro, has been not investigated yet. Growth and invasion of HCT-8 tumor cell line was investigated in presence of TDO or/and IDO-1 inhibitors.

Results: TDO mRNA was expressed in HCT-8, HEP-G2, SK-MEL-28 tumor cell lines. Interestingly TDO was found for the first time in immunocompetent cells obtained ex vivo from human CD14+ cells, suggesting further investigations about its role in tumor biology and immune function. Pretreatment of HCT-8 cells with 680C91 and/or 1-methyl-dl-tryptophan, IDO1 inhibitor, concentration-dependently inhibited cell proliferation; MTT test confirmed the non-toxic effects of TDO and IDO1 inhibitors in tumor cell lines.

Conclusion: Our data highlight TDO involvement in in vitro tumor cell growth. A better knowledge of TDO expression and function in tumor microenvironment is necessary to develop TDO inhibitors, improving immune response and arresting cancer progression.