UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title

Do novel dual COX-2 inhibitors/TP receptor antagonists regulate the immune response in the tumor inflammatory microenvironment?

2)Abstract (max 500 words)

PD-L1 has a relatively ubiquitous expression potential in cancer cells, endothelial cells (ECs) and macrophages within an inflammatory tumor microenvironment (TME), and "hijacking" this potential appears to be a widespread mechanism exploited by tumors to evade immune surveillance. Consistently, high PD-L1 levels in distinct cell compartments (nucleus, membrane) as well as soluble/exosomal PD-L1 in may foster immune tolerance in cancer. Being at the cross-roads between inflammation and immunity, eicosanoids are key signaling molecules that may limit the efficacy of PD-1/PD-L1 immunotherapies in cancer. However, the mechanisms and targets of eicosanoid-mediated immunoregulation are not completely understood. Inhibiting eicosanoid signaling at different levels and in different cells of the TME could represent a valid chemotherapeutic strategy not only to control progression of COX-2-overexpressing cancer but also to enhance the response to immune therapies.

In the framework of a collaborative project, we recently developed novel dual NSAIDs acting as selective COX-2 inhibitors and platelet TXA_2 receptor antagonists in the nM range with improved pharmacological profile with respect to available NSAIDs. We recently provided the first evidence that the endothelium is a source of soluble PD-L1, which is secreted in response to inflammatory stimuli. Moreover, preliminary data show that PD-L1 expression in response to inflammatory agents is downregulated by selected novel COX-2 inhibitor/TP antagonists in endothelial and cancer cells. Based on the above background and on our preliminary data, we hypothesized that COX-2 derived PGE_2 and/or TXA_2 would affect PD-L1 expression and trafficking in endothelial and breast cancer cells within the TME, and that blocking their signaling would enhance immune response to tumors.

Therefore, **the general objective** of this project is to profile the immunoregulatory potential of dual COX-2 inhibitors/TP antagonists in distinct cell types of the inflammatory TME. An additional aim of the project is to further characterize the endothelium as a source of extracellular PD-L1 and, more generally, as an immunological barrier. Specifically, we will investigate the mechanisms involved in the regulation of PD-L1 expression and trafficking by PGE_2 and TXA_2 using selected novel dual COX-2 inhibitors/TP antagonists as well as other pharmacological (e.g. glucocorticoids) and RNA-based approaches as controls.

We anticipate to unravel the specific contribution of COX-2-derived PGE_2 and TXA_2/TP signaling to PD-L1 trafficking. The exosome PD-L1 content from endothelial and cancer cells and its functional role in effector immune cells will also be assessed.

The proposed research could have a substantial impact on the field in several ways. The anticipated output includes reinforcing the basis for using anti-inflammatory agents in combinatorial anticancer strategies with chemotherapeutics and/or immune checkpoint inhibitors.