ImmunoTools IT-Box-Cy55M-Award 2013

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Role of microsomal PGE synthase 1 and its impact on carcinogenesis:

The lipid mediator prostaglandin E2 (PGE_2) controls a variety of physiological processes, ranging from initiation of inflammatory processes to promotion of wound-healing and angiogenesis. During cancer progression, chronic inflammation constitutes a regular feature of the local tumor microenvironment. Cyclooxygenase 2 (COX-2) is believed to promote cancer development by producing excess amounts of PGE_2, thereby acting as a master regulator of inflammation. Blocking COX-2 significantly prevents inflammation and cancer derived from a variety of different entities (Harris, 2009). Since inhibition of COX-2 bears known cardiovascular risks (Catella-Lawson, 2001), alternative targets have to be found to abolish ill-regulated PGE_2 synthesis in cancer patients. Microsomal PGE synthase 1 (mPGES-1) serves downstream of COX-2 to convert PGH_2 to PGE_2, providing an attractive target for future therapy approaches. Amidst an array of different cell types expressing mPGES-1, cells of the myeloid origin e.g. monocytes, macrophages and dendritic cells are among the most important sources for PGE_2 synthesis and thus are incriminated to play a pro-tumorigenic role in this scenario. By using a tumor model, in which mice develop spontaneous tumors, we want to link processes in which mPGES-1-derived PGE_2 is accumulated with tumor promoting mechanisms in vivo. Hence, we will isolate different myelocyte subsets out of tumors from wild type or mPGES-1 deficient tumor bearing mice via fluorescence activated cell sorting (FACS). This enables further studies, which include characterization of gene expression and expression of signature polarization markers on the cell surface. Additionally, co-culture of these cells with splenic T cells gives us the opportunity to study the capacity of myelocytes to mediate T_H1 responses and to induce cytotoxic activity in T cells. Thus, we want to clarify in these co-culture experiments how exactly PGE_2 impacts plasticity and activity of naïve and pre-polarized T cells. The *IT-BOX-Cy55M* from ImmunoTools offers a wide spectrum of cytokines, which alter immune responses. Thus, by adding single cytokines or as a combinational cocktail into co-culture experiments, we are able to investigate how PGE_2 augments or blunts specific cytokine signaling. These approaches will strengthen our understanding of how mPGES-1-derived PGE_2 aids tumors in escaping immune recognition.

References:

Harris RE. Cyclooxygenase-2 (cox-2) blockade in the chemoprevention of cancers of the colon, breast, prostate, and lung. Inflammopharmacology 2009;17:55-67

Catella-Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, Vyas SN, FitzGerald GA. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 2001;345:1809-17