ImmunoTools *special* Award 2016

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Impact of hexosamine pathway on immunomodulation in colorectal cancer

Deregulated cellular metabolism is a hallmark of tumors. Cancer cells increase glucose and glutamine flux to provide energy needs and macromolecular synthesis demands. Several studies have been focused in importance glycolysis and pentose phosphate pathway. However, a neglected but very important branch of glucose metabolism is the hexosamine biosynthesis pathway (HBP). The HBP is a branch of the glucose metabolic pathway that consumes approximately 2–5% of the total glucose and glutamine, generating UDP-GlcNAc as the end-product. UDP-GlcNAc is the donor substrate used in multiple glycosylation reactions.

Our previous work suggests that the metabolite availability to the hexosamine pathway induces aberrant cell glycosylation that provokes morphologic changes and increased cell migration *(Alisson Silva Plos One, 8: e60471, 2013)*. These results have being corroborated by a mouse model of syngeneic colon carcinoma cells (MC38). In this model, metabolite availability to the HBP was induced by selective destruction of β pancreatic cells through treatment of C57BL/6 with streptozotocin (STZ) leading hyperglycemic mice. STZ treated mice showed a significantly enhanced growth of subcutaneous MC38 tumors. Metastatic colonization of the lung was also increased in STZ treated animals. Histochemistry of tumors demonstrated an increment of glycoconjugates containing α2-6sialic acid, the most common aberrant glycosylation on cancer cells. Hypersialylation of $CD8^+$ T cells was also observed in the blood of STZ treated mice. Noteworthy is that tumors of STZ treated mice also showed a higher number of M2 polarized macrophages. These results put forward the hypotheses that HBP links the altered metabolism with aberrant glycosylation providing a mechanism of how cancer cells can sense and respond to microenvironment changes.

With the main purpose of studying the role of cellular glycosylation in tumor progression, in this work we will analyze the impact of hyperglycemia (HG) in

immunomodulation of murine colon carcinoma cells (MC38) *in vivo*. We aim to examine the role of hypersialylation on $CD8^+$ T cells function regarding cytokine production, cell recognition and cytolytic activity. Furthermore influence of HBP on macrophage polarization will be studied.

We further aim to delineate the mechanistic implication of hypersialylation due to hyperglycemia by employing genetic models including selectin deficient mice. Thus, metastasis in hyperglycemic mice will be studied in the background of P- and L-selectin deficient mice. Taken together, these experiments will provide evidence, if sialic-acid binding receptors are potential targets to interfere with cancer progression and could support the rationale to develop agents to block such receptors for cancer therapy. Selected reagents from ImmunoTools will be used for differentiation of mice bone marrow, and for analyzes of CD8 T cells responses.

ImmunoTools *special* AWARD for **Adriane Regina Todeschini**

includes 17 reagents

recombinant human cytokines: rh Galecin-1, rh Galecin-3

FITC - conjugated anti-mouse CD3, CD25, CD45, CD62L, Isotype control

PE - conjugated anti-mouse CD8, CD11b

APC - conjugated anti-mouse CD4, CD44, Gr1, NK

recombinant mouse cytokines: rm IFN-gamma, rm IL-4, rm M-CSF, rm TNF-alpha

DETAILS more AWARDS