SHAPING THE IMMUNOMETABOLISM OF HR+ BREAST CANCER WITH KYNURENAMINES


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Background Hormone receptor positive breast cancer (HR+ BC) is the most common type of BC, causing most BC-related deaths among women. Considerable progress has been achieved over the past three decades in clinical BC management, such the use of CDK4/6 inhibitors combined with endocrine therapy. Unfortunately, lack of response to immune checkpoint blockers (ICB), acquired resistance to CDK4/6i together with metastatic disease remains a major challenge for these patients; around 70% of women ultimately progress and succumb to this devastating disease. Thus, despite the significant advances, there is a largely unmet medical need for women with HR+ BC. In recent years, additional approaches to target not only new co-stimulatory/inhibitory receptors but also tumor or infiltrating immune cells metabolic pathways has been put forward.

This proposal is based on the premises of our previous own discovery where a novel biogenic amine 3-hydroxy-L-kynurenamine (3HKA) has potent anti-inflammatory effect on several preclinical models of autoimmune diseases.1 3HKA is the third (together with serotonin and melatonin) biogenic amine produced by an uncharacterized lateral branch of the tryptophan catabolism pathway. It is released by both professional and non-professional antigen-presenting cells during inflammatory conditions and spontaneously released by several cancer cell lines including HR+ BC cell line TS/A.

Methods Aimed at investigating the effect of 3HKA on HR+ BC tumor incidence and growth, we performed a series of in vivo experiments harnessing a DMBA-induced MPA-accelerated endogenous model of HR+ BC2 both in immunocompetent and immunocompromised mice.

Results Preliminary results demonstrate that 3HKA (1) Delays tumor onset (2) Decreases tumor growth (3) Prolongs survival rate (4) Decreases tumor grade as determined by histological analysis. In vitro and ex vivo experiments demonstrate that 3HKA affects cell cycle progression on tumor cells and T. On T cells, 3HKA modifies cell proliferation and exhaustion profile as determined by multiparametric flow cytometry.

Conclusions This project undercovers a new treatment strategy by targeting the recently defined lateral pathway of tryptophan catabolism. This approach focuses in the individual metabolic effect on each cell type building the tumor microenvironment. Ultimately, the knowledge generated from this project will open the door for new therapeutic combinations with radiotherapy, ICB, iCDK4/6 and endocrine-based therapies improving patient options.

REFERENCES