ID: 00959
Type: Poster
Topic: Tumor treatment

THE IMPACT OF INFLAMMASOME INHIBITORS IN MACROPHAGE DIFFERENTIATION AND TUMOR PROGRESSION.

Paula María Soriano Teruel[1] , María Jesús Vicent[2] , Mar Orzáez Calatayud[1]

1) Laboratory of Peptide and Protein Chemistry, Centro de Investigación Príncipe Felipe 2) Laboratory of Polymer Therapeutics, Centro de Investigación Príncipe Felipe

INTRODUCTION. The tumor microenvironment (TME) and, in particular tumor-associated macrophages (TAMs) play crucial roles in breast cancer (BC) progression and metastasis. however, the endogenous regulatory mechanisms underlying TAM differentiation remain largely unknown. Macrophage subpopulations have been described as classically activated (M1), possessing proinflammatory and tumoricidal capabilities or alternatively activated (M2), suppressing inflammation and making the endothelium more susceptible to tumor cell invasion and metastasis. However, inflammation has controversial roles in tumor progression. Despithe the fact M1 macrophages are considered tumoricidal in early stages, studies suggest that the reduced release of pro-inflammatory cytokines (e.g. IL-1β) decreases tumor progression and metastasis in advanced breast cancer. As TAMs are heterogeneous and evolve during breast tumor development, their contribution to tumor progression remains to be clarified. Macrophage differentiation is controlled by the inflammasome (4); a macromolecular complex of the innate immune system responsible for the activation of the protease procaspase-1 (PC1). Once activated, PC1 processes the pro-IL1-βand -IL-18 cytokines released to induce inflammation. We have identified a new inflammasome inhibitor, QM-378 (QM) that inhibits inflammasome assembly, thereby preventing release of pro-inflammatory cytokines.

OJECTIVES. In this study, we propose to use new this inflammasome inhibitoras chemical tool to specifically target the inflammasome to fully understand its role in macrophage differentiation and in breast tumor progression.

METHODOLOGY. In this work, the characterization of the activity of the inflammasome inhibitor was carried out in cellular models of inflammation in monocytes and macrophages M0 and M1. On the other hand, we had studied the role of the inhibitor QM-378 in the process of differentiation of macrophages M1 and its influence on the migration of metastatic breast cancer.

RESULTS AND CONCLUSIONS. The inflammasome inhibitor QM378 decreased the release of pro-inflammatory cytokines (such as IL1-β) from M1 macrophages and interfered with macrophage differentiation. Moreover, breast cancer cell-migration assays using the secretome from M1 macrophages as a pro-inflammatory stimulus have demonstrated that drugs targeting the inflammasome decrease cell migration. These preliminary studies consolidate the specific inhibition of the inflammasome in macrophages from the TME as a robust strategy to inhibit tumor metastasis and paves the way to employ rationally designed polypeptide-based nanoconjugates to specifically target the inflammasome of TAMs to fully understand its role in breast tumor progression.

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