Identification of a new molecular target to prevent metastatic dissemination of breast cancer cells exposed to cl-CD95L

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Breast cancers represent a heterogeneous pathology, which can be classified as Triple-negative breast cancers (TNBC), non-TNBC and HER2+. TNBCs are characterized by a negative immunohistochemical staining for estrogen (ER) and progesterone (PR) receptors and human epidermal growth factor-2 (HER2). Metastases and relapses remain more frequent in TNBC patients than in Non-TNBC women due to the aggressiveness of these tumors and the lack of tailor-made therapeutic treatment options. Therefore, identification of new therapeutic targets for TNBCs is of crucial interest. Our group works on the so-called death receptor CD95 known to initiate apoptosis by interacting with its ligand CD95L. CD95L is a transmembrane ligand (m-CD95L) that can be cleaved by metalloproteases. We recently showed that unlike m-CD95L, the naturally-processed CD95L (cl-CD95L) is a potent prognostic marker of metastatic dissemination in TNBC women. Furthermore, we demonstrated that cl-CD95L promotes TNBC cell migration through induction of an “unconventional” PI3K/Akt/mTOR signaling pathway. To block this non-apoptotic signaling pathway, we attempted to generate in collaboration with modelers and chemists, an inhibitor of the PI3K/mTOR pathway. From a chromene backbone and multiple rounds of in silico/in vitro and in cellulo drug screening, we identified a molecular lead designated DHM25 that showed a strong anti-tumor activity against breast tumor cells. A large-scale kinase assay against the human kinome revealed that DHM25 turned out to be a selective and potent mTOR inhibitor. In summary, we have designed and synthesized a potent and covalent mTOR inhibitor that represents a very attractive therapeutic agent to impair CD95-mediated cell motility in TNBC cells and, by doing this, to reduce the risk of metastatic dissemination in these women.

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Broad spectrum anticancer activity of pistagremic acid

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Pistagremic acid was isolated from the chloroform fraction of *Pistacia integerrima* by anticancer activity guidance, and the chemical structure was identified as 3-methyl-7-(4,4,10,13,14-pentamethyl-3,2,3,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthryl-17-yl)-oct-3-enolic acid by NMR and X-ray crystallography analysis. Cytotoxic evaluation against NCI-60 DTP human tumor cell line was performed which showed broad spectrum antiproliferative activity with an average GI50 and TGI, values 0.103 µM and 0.259 µM, respectively. It also showed significant LC50 value at the average 0.634 µM against all cell lines excluding K-562, RPMI-8226, NCI-H226, and NCI-H460 cell-lines and pistagremic acid may serve as a potential structure lead for the development of new anticancer drugs.

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