Small Molecule inhibition of cathepsin L and K as potential therapeutics for macrophage driven breast cancer

We hypothesize that cathepsin L plays a role in the macrophage contribution to the metastatic phenotype of breast cancer.

Tumor-associated macrophages secrete many factors including proteases and growth factors, which ultimately promote the metastatic phenotype of mammary tumors. Due to their numerous pro-tumor functions, tumor-associated macrophages represent an attractive cell population for stromal-targeted anti-cancer therapies. Interleukin-4 stimulation promotes macrophage differentiation from a baseline M0 state to a more pro-tumorigenic M2 phenotype, which is often associated with increased expression of proteases including the lysosomal cathepsin L. Cathepsin L is important in both macrophage and tumor cell invasion, whereby secreted cathepsin L degrades the extracellular matrix allowing for cell infiltration. M0 to M2 differentiation was not accompanied by an overall increase in the protein expression of cathepsin L, however, secreted cathepsin L was increased in the M2 macrophage population.

The present study examined the role of cathepsin L in M0 to M2 differentiation and macrophage-mediated tumor cell invasion using the novel cathepsin L/K inhibitors KGP94 and KGP207 [Dr. Kevin Pinney, Baylor University]. Boyden chamber assays revealed that KGP94 and KGP207 prevented in vitro M2 macrophage invasion and reduced macrophage-stimulated invasion of 4T1 murine breast cancer cells. KGP94 and KGP207 treatment also partially prevented IL-4-stimulated M0 to M2 differentiation of macrophages as determined by a decrease in the IL-4-induced expression of the M2 marker Arginase-1 upon drug treatment. Furthermore, exogenous recombinant cathepsin L partially stimulated the expression of Arginase-1 in M0 macrophages. Together, these data suggest that cathepsin L may play a role in macrophage M0 to M2 differentiation.

In summary, the novel cathepsin L/K inhibitors KGP94 and KGP207 altered M0 to M2 differentiation, reduced macrophage invasion, and reduced macrophage-stimulated invasion of breast cancer cells. These data highlight the importance of cathepsin L in macrophage functions and suggest that cathepsin inhibition strategies may be therapeutically beneficial by impairing the progression of tumors, particularly those with high recruitment of M2 macrophages.