Development of a Photocaged Cathepsin B Inhibitor With Increased Lysosome Uptake and Light-activated Biological Functions

Lin, Jasmine (School: Taipei First Girls High School)

Cathepsin B in lysosome is a cysteine protease that plays an important role in various pathological processes including many cancers. Therefore, it is a cancer protein biomarker. A method to control the activity of unregulated cathepsin B promotes the understanding of its role in various biological pathways. Eventually, it could lead to therpeutic solutions of cancer. Ac-LVK-CHO is a tripeptide inhibitor that can control cathepsin B activity. However, the aldehyde group of Ac-LVK-CHO is unstable, which hampers its applications. In order to address this problem, a photocaged 2-nitrobenzyl group is introduced to protect the aldehyde functional group. After entering the cell, the 2-nitrobenzyl group can be deprotected upon UV light irradiation, restoring the inhibition of Ac-LVK-CHO on cathepsin B. Moreover, a targeting group morpholine is also introduced on Ac-LVK-CHO to increase lysosome uptake of the inhibitor. In this study, I have synthesized the inhibitor Ac-LVK-CHO and modified it with the photocaged 2-nitrobenzyl group and the targeting group morpholine to form the dual caged inhibitor Ac-LVK(EMOR)-2NB. It is decomposed within 30 seconds, and fully converted into Ac-LVK-CHO after 2 minutes of irradiation. Ac-LVK(EMOR)-2NB is stable in pH 4 and pH 9 conditions without irradiation and inhibits cathepsin B after irradiation. Furthermore, in Hela cells, after irradiation, the dual caged inhibitor can inhibit cellular cathepsin B. In addition, the dual caged inhibitor can be better directed into lysosome. Through spatial and temporal control by irradiation, this dual caged inhibitor, Ac-LVK(EMOR)-2NB, can be used as a tool for investigating different scientific categories, such as cell heterogeneity and single-cell biology.