The Natural Product 3',4',7,8- tetrahydroxyflavonoid Is a Potent BRD4-BD2 Inhibitor in Suppressing Acute Myeloid Leukemia

Jiao Li[1], Wei Zou[1], Koukou Yu[1], Bing Liu[1], Weifeng Liang[1], Lisha Wang[2], Yin Lu[1], Zequn Jiang[1], Aiyun Wang[1], and Jiapeng Zhu[1]

[1]Nanjing University of Chinese Medicine
[2]PharmaBlock Sciences Nanjing Inc

August 20, 2020

Abstract

Background and Purpose: Bromodomain-containing protein 4 (BRD4) binds acetylated lysine residues on the N-terminal tails of histones through two bromodomains (BD1 and BD2) to regulate gene transcription. Inhibiting one or both of the bromodomains results in different phenotypes, suggesting BD1 and BD2 may have different functions. Here we report the characterization of a natural product 3',4',7,8-tetrahydroxyflavonoid as a new and potent BRD4 inhibitor with anti-cancer activities in vitro and in vivo. Experimental Approach: AlphaScreen assays were performed to evaluate the inhibitory activities of 3',4',7,8-tetrahydroxyflavonoid against the bromodomains. Crystal structures of the compound bound to BRD4-BD1 or BD2 were solved to reveal key binding features. MV4-11 in vitro cell culture model and xenograft mouse models were used to examine the compound's anti-cancer activities. Western blotting, Immunofluorescence staining and RT-PCR were used to investigate the mechanism(s) of the compound in suppressing MV4-11 cell and tumor growth. Key Results: 3',4',7,8-tetrahydroxyflavonoid is ˜100-fold more selective for BRD4-BD2 (IC50=204 nM) than BD1. Co-crystal structures show 3',4',7,8-tetrahydroxyflavonoid establishes more interactions in BRD4-BD2 acetylated lysine binding pocket than BD1. Consistent with a selective and high affinity with BRD4 bromodomains, 3',4',7,8-tetrahydroxyflavonoid treatment inhibited MV4-11 cell growth and reduced AML tumor growth in vitro and in vivo, respectively. Conclusion and Implications: Our data suggest 3',4',7,8-tetrahydroxyflavonoid as a potent selective inhibitor of BRD4-BD2 with a novel chemical scaffold. Given its distinct chemical structure from current BRD4 inhibitors, this compound may open the door for a novel class of BRD4 inhibitors by serving as a lead compound.

Hosted file

`ready_to_upload_version_2.pdf` available at https://authorea.com/users/352372/articles/476667-the-natural-product-3-4-7-8-tetrahydroxyflavonoid-is-a-potent-brd4-bd2-inhibitor-in-suppressing-acute-myeloid-leukemia