Dynamic Combinatorial Chemistry for the Discovery of Arkadia-Targeting Cyclopeptides for Cancer Therapy

Abstract :

The TGF-β pathway is a relevant therapeutic strategy under investigation for the treatment of various cancer. Different compounds that inactivate either TGF-β or its receptors have been developed to block this pathway. However, alternative strategies that would elicit a more selective inhibition such as those targeting downstream effectors of the canonical TGF-β pathway are being actively pursued to reduce the toxicity of these treatments. Arkadia is a downstream effector that activates the TGF-β signaling pathway *via* its ubiquitin ligase activity. This activity relies on the interaction of its RING domain with the E2 enzymes. Inactivation of this interaction therefore constitute an interesting therapeutic target. However, because of the challenging protein-protein interaction interface (large, hydrophobic and with discontinuous epitope) between Arkadia and the E2, no inhibitor has yet been identified. In this project, we intend to take advantage of our recent characterization of a direct inhibitor of the Arkadia RING domain to generate stable cyclopeptides mimetic as inhibitor of the Arkadia/E2 enzyme protein interaction. In that aim, we will exploit a newly developed strategy based on the self-assembly of conformationally stable peptides guided by their molecular recognition by a biological target. For this purpose, dynamic combinatorial chemistry (DCC) will be used to decorate a small folded peptide scaffold with functional groups involved in the recognition of a relevant target, allowing the rapid access to a large and complex library of well-ordered protein mimetic that are in equilibrium with each other and can be screened in a single step toward a relevant protein. We believe that the combination of a rationally designed folded structure and the self-evolutionary nature of the functionalization method could lead to the identification of specific inhibitory peptides for Arkadia ubiquitin ligase activity with anti-TGF-β therapeutic potential.