Optimization of small molecule inhibitors targeting the SIRPα-CD47 immune checkpoint

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In order to survive in the body, cancer cells have to develop ways to avoid the immune system. One of them involves the SIRPα-CD47 immune checkpoint. CD47 is a ubiquitous cell-surface receptor protein expressed in most cell types. It binds to SIRPα, an immunoglobulin-like counter-receptor, at the surface of macrophages where it regulates the decision process of eliminating the targeted cell through phagocytosis, thus acting as a so called "don't eat me" signal. Physiologically, this signal helps to prevent undesired disposal of healthy cells. However, some cancer cell lines hijack this pathway by overexpressing CD47 thus halting phagocytosis and allowing their survival. A small molecule able to disrupt the SIRPα-CD47 protein-protein interaction would then be an interesting drug candidate to enhance the activity of existing anti-cancer chemotherapy.

To this extent, a structure-based hit-to-lead approach is used (DOTS[1]), where hit compounds binding SIRPα identified from screening are systematically optimized into a lead compound. The validated hits target a cryptic pocket in an open state of SIRPα revealed by the outward tilt of the Gln52 of the C'D loop at the interface between SIRPα and CD47. This hindered experimental evaluation of the early low affinity hits as they had to compete with the Gln52 to induce the open conformation. Our team has undertaken 2 strategies to overcome the challenges of refractory SIRPα conformations and generating higher affinity molecules. (1) To lower the complexity of the system, constitutively open mutants (Q52K, Q52R) were developed to more rapidly advance candidate molecules. (2) More efficient optimization toward higher affinity molecules is enabled by ChemoDOTS, a recently published webserver[2] available at https://chemodots.marseille.inserm.fr/ which aims to produce *in silico* focused libraries of synthetically available compounds derived from a starting activated fragment. A virtual screening followed by synthesis and experimental validation is then performed to select the best products, that can go through a new round of optimization. For now, this approach allowed us to find molecules that reach 10 µM IC50 for the disruption of the SIRPα-CD47 complex.

Bibliography

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