

Antineoplastic targeted therapy: Identifying and manipulating cancer associated fibroblasts (CAFs) with aberrant mechanotransduction

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The tumor microenvironment (TME), composed of resident and infiltrating stromal cells, plays a crucial role in tumor progression, metastasis, and therapeutic resistance. Among these stromal cells, cancer-associated fibroblasts (CAFs), particularly those activated by mechanical cues (myCAFs), are key modulators of the TME. These CAF subsets present aberrant activation of the YAP, a transcriptional co-activator in the Hippo pathway, that promotes CAF-dependent extracellular matrix (ECM) stiffening, cancer invasion, and angiogenesis. However, the lack of specific markers for aggressive CAFs hinders the development of targeted therapies.

We hypothesize that aggressive CAFs with elevated mechanotransduction activity—characterized by activated YAP (Yes-associated protein) signaling—express distinct membrane epitopes that could serve as specific biomarkers. Thus, YAP regulates membrane proteins in aggressive CAFs either transcriptionally or via post-translational modifications, altering their structure and surface presentation. To test this, we employ SELEX (Systematic Evolution of Ligands by Exponential Enrichment) to identify aptamers that bind selectively to these epitopes.

To distinguish YAP-high aggressive CAFs from their less aggressive counterparts, we engineered a murine CAF line with inducible YAP degradation via degron tag. Functional validation (Western blot, qPCR, ECM remodeling, and luciferase assays) confirmed reduced YAP activity, providing a model for SELEX. Identified aptamers will be used to isolate membrane targets via immunoprecipitation or mass spectrometry.

Our long-term goal is to functionalize these aptamers with lipid-polymer nanoparticles (LPNPs) for targeted delivery of a YAP-specific PROTAC (YAP-PROTAC), aiming to reprogram aggressive CAFs toward an anti-tumor phenotype. For that, we propose to identify YAP-specific aptamers using protein-SELEX on recombinant YAP. Altogether, this approach may offer a novel strategy to specifically modulate aggressive CAFs, reducing off-target toxicity and potentially improving therapeutic outcomes.