PRINCIPE FELIPE
CENTRO DE INVESTIGACION

PhD Thesis Defense

POLYMER-BASED COMBINATION CONJUGATES FOR THE TREATMENT OF TRIPLE NEGATIVE BREAST CANCER: FROM RATIONAL DESIGN TO PRECLINICAL EVALUATION

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Abstract: Among breast cancer subtypes, triple negative breast cancer (TNBC) represents around 15-20% of newly diagnosed cancer cases. The lack of hormonal receptor (ER, PR, and HER2) expression impedes the administration of targeted therapies, and for this reason, the development of novel therapies for TNBC represents a primary clinical need.

Studies employing animal models of disease allow for the understanding of disease development and progression, the search for therapeutic targets, and the validation of therapeutic strategies; however, the lack of accurately characterized research models frequently hampers research aims. We present the detailed characterization of preclinically relevant spontaneously metastatic TNBC murine models that faithfully reproduce the human clinical scenario. Our comparisons have uncovered descriptors regarding the interconnected tissular/molecular processes driving disease progression towards metastasis, including metastatic spread via the lymphatic route, immune system remodeling, cancer-associated adipocytes, and crucial metabolomic alterations.

As part of the development of a polymer-based therapy for TNBC, we present a versatile and straightforward methodology for the preparation of well-defined polyglutamate-based drug combination conjugates based on the well-established properties of the poly-glutamic acid (PGA) as a multivalent and biodegradable polymer carrier. We synthesized and characterized a family of conjugates containing amino acid-based proteolytic drug linkers as key drivers in the final macromolecule solution conformation and biological fate. These new drug delivery systems incorporate both chemotherapy (Dox) and endocrine therapy (the aromatase inhibitor AGM) as a synergistic combination. Overall, we demonstrate how the presence of a small flexible Gly linker can modify the spatial conformation of the entire polymer-drug macromolecule, promoting the synergistic release of both drugs and significantly improving the biological activity.

In order to improve drug release intracellularly but also at the tumor microenvironment, we developed a new family of conjugates incorporating the pH-sensitive hydrazone linker. These conjugates provided improved antitumor and antimetastatic activity (supported by histology and transcriptomic analysis); however, we noted that the pH-sensitive drug-linker length significantly influences the cell death mechanism involved. Finally, we applied the knowledge acquired from the development of the previous polymer-drug combination conjugates, with the selection of a more powerful combination of synergistic drugs for TNBC treatment (including a tyrosine-kinase inhibitor, TKI and a topoisomerase inhibitor, TI) for the development of a more effective family of polymer-drug conjugates. This novel system demonstrated enhanced antitumor and antimetastatic activity. Overall, the findings exhibited throughout this Thesis highlight the need for a deeper understanding of polymer-drug conjugates at supramolecular level, including the need for a complete physicochemical characterization to allow the design of more effective polymer-drug conjugates.

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