New RNA-based therapeutic strategies to overcome chemoresistance in colorectal cancer

Colon cancer is one of the leading causes of cancer-related deaths worldwide. The development of drug resistance is the most common cause of colon tumor recurrence; how to overcome it is a key issue for cancer treatment. Cancer therapy frequently fails because the tumor does not express the drug's target. In order to enhance therapeutic response and overcome chemoresistance, specific, non-expressed genes can be successfully introduced into tumor cells using gene therapy. Our research group has shown that nucleolar stress, a process mediated by nucleolar proteins and some ribosomal proteins (rp), plays a crucial role in the 5-FU response. Among these rp, we identified uL3 as a key player in the cell response to 5-F. In studies involving a cohort of CRC patients, our group has shown that negative regulation of uL3 expression is associated with a poor prognosis and chemoresistance. In the laboratory, a CRC cell line silenced for uL3 that is resistant to the most common chemotherapeutics has been created. In this context, the present research project has two objectives: a) examining the biochemical pathways in which uL3 is involved in order to find new potential drug targets for overcoming chemioresistance; and b) developing a new therapy for the treatment of CRC based on the mRNA encoding for uL3. The experimental models used will be 2D and 3D systems and the in vivo CAM system (chicken embryo chorion-allantoic membrane). CAM is a simple, inexpensive, and extremely versatile model that can be used to test the activity, mechanism of action, and possible therapeutic synergism of an mRNA drug and classic chemotherapeutics.

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