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KEYWORDS – Homologous Recombination, Peptide therapeutics, Cell-penetrating peptides

MAIN FIELDS OF RESEARCH

Efficient DNA repair mechanisms are pivotal to counteract genomic instability, a hallmark of almost all cancer cells. DNA double-strand breaks (DSBs) are the most hazardous lesions a cell can encounter as a single unrepaired DSB leads to cell death, whereas erroneous repair results in mutations, which in turn can promote carcinogenesis. On the other hand, conventional cancer treatment by radiotherapy and certain chemotherapeutic drugs takes advantage of the cytotoxic properties of DSBs. However, these agents often lack selectivity for tumor cells, resulting in severe side effects for the patients, thus compromising their therapeutic potential. Hence, new strategies are key to the development of novel compounds that display synergistic effects with standard anti-cancer drugs by specifically targeting DSB repair mechanisms. In particular, homologous recombination (HR) as a repair mechanism for DSBs is indispensable for cancer cell survival. Importantly, the function of BRCA2 and CtIP, two critical HR factors, strongly relies on protein-protein interactions (PPIs). Consequently, specific targeting of these PPI interfaces could significantly improve the efficacy of conventional anti-cancer therapies. However, inhibition of PPIs has proven challenging as PPI interfaces commonly do not support binding of small drug-like molecules. In contrast, peptide-based inhibitors of PPIs are considered more promising but their therapeutic use is frequently limited by conformational and proteolytic instability as well as cell membrane impermeability. Importantly, artificial backbone modifications and the use of cell-penetrating peptides (CPPs) as delivery vectors were shown to significantly improve pharmaceutical properties of peptides.

In this project, we will apply those strategies in order to design potent peptide-based HR inhibitors targeting BRCA2 and CtIP, opening up new therapeutic avenues to combat cancer.

SPECIAL TECHNIQUES AND EQUIPMENT

Recombinant DNA technology, protein purification, chromatography, SPR, fluorescence polarization, circular dichroism, cell culture, confocal microscopy, flow cytometry