Radiation and targeted therapy combined approach in metastatic breast and prostate cancers – computational and biological evaluation

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Abstract

Breast cancer (BC) is estimated to have the highest incidence worldwide, while prostate cancer (PC) is the fourth most common cancer worldwide. The 5-year survival rate for patients with metastatic BC and PC is around 29%.[1] The combined use of radiotherapy (RT) and chemotherapy has shown promising effects in the treatment of metastatic cancers. When it comes to radiation, proton therapy, specifically, is expected to result in a decrease in the effect on the healthy tissues surrounding the tumor, compared to conventional radiotherapy.[2]

This study aims to address the current medical challenge in treating metastatic cancers by developing multiple approaches to enhance the apoptosis of cancer cells that overexpress CXCR4 and HER2. A deeper understanding of the reactive oxygen species (ROS)-mediated signals induced by RT at selected cell receptors is crucial for optimizing cancer treatment.

In the computational approach, we will perform molecular dynamics (MD) simulations to study the behavior of ROS with the receptors in the presence and absence of chemotherapy drugs (AMD3100 for CXCR4 and Trastuzumab for HER2) at the atomistic level. This will also provide insight into the extent of the interaction between the receptor and its antagonist/ligand.

We first studied the interaction between the target receptor CXCR4 and its specific inhibitor AMD3100. Molecular docking was performed with AutoDock Vina using the structure of CXCR4 (PDB-ID:3ODU)[3] and an optimized AMD3100 structure. From the docking output, the more stable complex was selected based on the binding affinity score provided, and 300 ns of MD simulation was performed by GROMACS 2018.44[4]. The simulation analysis was assessed by calculating the root mean square deviation (RMSD) and root mean square fluctuation (RMSF) and the radius of gyration calculations and contact point measurements with GROMACS functions. The intermolecular distances were computed using the VMD software[5].

Experimentally, the expression of the receptors in cell lines of interest representative of the 2 cancers (MDA-MB-231, MCF7, and SKBR-3 BC cell lines; DU145, PC3, and VCaP PC cell lines) was assessed by western blotting, and the therapeutic efficacy of photon-RT was assessed by evaluating cell viability *in vitro* in PC cell lines.

Computational results suggest the overall stability and proper equilibration of the CXCR4/AMD3100 complex, preserving structural integrity in functionally important areas of CXCR4. Experimentally,

protocols for viability assessment after irradiation were established, and under the conditions tested, no decrease in cell viability was observed in PC cell lines.

In addition, Monte Carlo simulations with the TOPAS-nBio (v2.0) toolkit are underway to characterize the ROS induced by different radiation types (protons and photons), which will serve as input for MD simulations that will characterize ROS-receptor interactions.

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