ABSTRACT

The evolving knowledge about the role of protein-protein interactions in organisms has opened new therapeutic possibilities. One of the areas that has attracted attention is the blockade of immune system checkpoint proteins, such as PD-1/PD-L1. Utilizing these checkpoint proteins is a common strategy that allows cancer cells to evade detection and proliferate within the human body. This strategy involves suppressing the activation of T lymphocytes, leading to negative regulation of the immune system response. Therefore, blocking the PD-1/PD-L1 interaction holds promise in cancer treatment. Nevertheless, it is not a trivial task, mainly due to the large, flat, and hydrophobic interaction surfaces between these proteins, which lack significant clefts that would facilitate inhibitor design. So far, the FDA has approved seven PD-1/PD-L1 interaction inhibitors based on antibodies. Unfortunately, antibody-based therapies have limitations, such as potential immunogenicity and poor penetration into solid tumors. Hence, research is ongoing into other groups of potential inhibitors. Among them, small molecules and peptides stand out, which, in comparison to antibodies, may offer lower toxicity, better bioavailability, and more effective penetration into solid tumors. However, low-molecular-weight compounds, despite their significant diversity and modifiability, have certain size-related limitations, meaning they are too small to effectively block extensive protein-protein interaction surfaces. Peptide-based drugs seem to strike a balance, as their size allows them to efficiently inhibit protein interactions while retaining the advantages typical of smaller molecules.

Particularly promising in blocking protein-protein interactions are miniproteins, which combine the characteristics of peptides and proteins. These molecules have stable tertiary structures and a mass of up to 10 kDa. Their small size allows for production through chemical synthesis, facilitating the introduction of noncanonical amino acid residues and expanding their potential functional range. On the other hand, a sufficiently long amino acid sequence enables modifications that enhance their activity without significantly altering the tertiary structure. Miniproteins hold promise for medical applications, especially for challenging therapeutic targets, such as blocking protein-protein interactions. The aim of this thesis was to develop inhibitors of the PD-1/PD-L1 interaction based on miniproteins.