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A Study on the Interaction between Human Serum Albumin (HSA) and Fibroblast Activation Protein Inhibitor (FAPi): Experimental and Theoretical Perspectives

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Abstract

Fibroblast activation protein (FAP) is a membrane-bound protease that has limited expression in normal adult tissues but is highly expressed in the tumor microenvironment of many solid cancers. Among them, a class of FAP inhibitors (FAPi) with a N-(4-quinolinoyl)-Gly-(2-cyanopyrrolidine) scaffold displayed nanomolar affinity and high selectivity against other interfering dipeptidyl peptidases and prolyl oligopeptidase. FAP-2286 is a FAP-binding peptide coupled to a radionuclide chelator that is currently being investigated in patients as an imaging and therapeutic agent. FAPI-46 is a quinoline-based fibroblast activation protein (FAP)-targeted radiotracer. FAPI-46 has higher tumor uptake and prolonged tumor accumulation. FAPI-46 can be used for tumor imaging of a multitude of different cancers[1-2]. In this study, FAPi-46 and FAP-2286, as well-known FAP inhibitor, were selected and prepared. Furthermore, the binding affinity between the above-mentioned inhibitors and human serum albumin (HSA) were studied under simulated physiological conditions (using molecular docking (MD)) and experimental analyses (using fluorescence and CD spectroscopies and cyclic voltametry). The obtained results revealed that the formation of a complex between HSA and drugs were responsible for quenching the native fluorescence of protein at 343 nm and can be illustrated by the static mechanism. The binding constant and number of binding sites were considered and proposed that the combination of hydrophobic and electrostatic forces were the principal intermolecular forces stabilizing the complex. Also, theoretical results show that the both of drugs have high affinity for binding to HSA.

Key words: FAP, human serum albumin, anticancer potential, molecular properties, molecular docking,

References

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