Universität Basel

Publication

Allosteric Binding Sites On Nuclear Receptors: Focus On Drug Efficacy and Selectivity

Nuclear receptors (NRs) are highly relevant drug targets in major indications such as oncologic, metabolic, reproductive, and immunologic diseases. However, currently, marketed drugs designed towards the orthosteric binding site of NRs often suffer from resistance mechanisms and poor selectivity. The identification of two superficial allosteric sites, activation function-2 (AF-2) and binding function-3 (BF-3), as novel drug targets sparked the development of inhibitors, while selectivity concerns due to a high conservation degree remained. To determine important pharmacophores and hydration sites among AF-2 and BF-3 of eight hormonal NRs, we systematically analyzed over 10 μ s of molecular dynamics simulations including simulations in explicit water and solvent mixtures. In addition, a library of over 300 allosteric inhibitors was evaluated by molecular docking. Based on our results, we suggest the BF-3 site to offer a higher potential for drug selectivity as opposed to the AF-2 site that is more conserved among the selected receptors. Detected similarities among the AF-2 sites of various NRs urge for a broader selectivity assessment in future studies. In combination with the Supplementary Material, this work provides a foundation to improve both selectivity and potency of allosteric inhibitors in a rational manner and increase the therapeutic applicability of this promising compound class.