ELECTROSTATIC INTERACTIONS AS DETERMINANT FOR IMATINIB’S AFFINITY TO KIT AND CSF-1R ONCOGENIC MUTANTS

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The receptors tyrosine kinase (RTKs) for the colony stimulating factor-1 (CSF-1R) and the stem cell factor (SCFR or KIT) are important mediators of signal transduction. The normal function of these receptors is altered by gain-of-function mutations that lead to their constitutive activation, associated with cancer diseases. A secondary effect of the mutations is the alteration of receptors’ sensitivity to tyrosine kinase inhibitors, such as imatinib, compromising effectiveness of these molecules in clinical treatment. The mutation V560G in KIT increases its sensitivity to imatinib, while the S628N and D816V, in KIT, and D802V, in CSF-1R, trigger resistance to the drug. Our goal in this work consisted in study the affinity of imatinib to the native (WT) and mutant forms of KIT (V560G, S628N and D816V) and CSF-1R (D802V). By means of docking, molecular dynamics simulations and energy calculations, the binding affinity of imatinib to the different targets was estimated and the \textit{in silico} predictions were correlated with the available experimental (\textit{in vivo} and \textit{in vitro}) data. The free energy of binding was highly correlated with the IC\textsubscript{50} values of inhibition and the energy decomposition into its different components evidenced the electrostatic interactions as the differential factor impacting the binding energy. The mutations D802V and D816V showed to be the most deleterious in the electrostatic energy contribution to the binding of imatinib, due to charges redistribution in the vicinity of the binding site. Our data also indicates that the JMR domain plays a minor role in the resistance mechanism. The study of CSF-1R and KIT in their WT and mutant forms in complex with imatinib complemented the early studies of the isolated receptors, showing that not only the conformational change induced by the oncogenic mutations, but also the electrostatic interactions and the protonation state of the ligand can explain the resistance phenomena.

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