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‘Piperazining’ the catalytic gatekeepers: Unveiling the mechanistic pan-inhibitory activities of masitinib towards SRC kinases; LYN, FYN and BLK, in the treatment of Diffuse Large B-cell lymphoma

Blocking the oncogenic signaling of B-cell receptor (BCR) has been recently explored as a viable therapeutic approach in the treatment of Diffuse large B-cell lymphoma (DLBCL), an aggressive form of Non-Hodgkin Lymphoma. This involves the multi-targeting of certain members of the SRC kinase family; LYN, FYN and BLK, which propagate BCR signals to downstream effectors. In a recent study, the pharmacological activity of masitinib was repurposed to ‘triple-target’ these SRC kinases. However, it was important to further understand the molecular mechanisms of selectivity and pan-inhibition demonstrated by masitinib to pave way for the design of potent pan-SRC kinase inhibitors. To this effect, we employed molecular dynamics simulation techniques to investigate the interaction dynamics of masitinib towards LYN, FYN and BLK coupled with the molecular basis of selectivity, pan-inhibition and high-affinity binding. Results revealed that, the mechanistic ‘pan-inhibitory’ activities of masitinib towards these SRC kinases entailed the initial selective targeting of catalytic “gatekeeper” residues (Asp334/Glu335 – LYN, Asp130/Asp148/Glu54 – FYN, Asp89 - BLK) and high affinity interactions, which involved strong hydrogen and ionic bonds formation coupled with salt bridges via its (masitinib) piperazine ring at the entrance of the catalytic pockets, followed by systematic access into the deep hydrophobic grooves and eventual disruption of catalytic (kinase) activities. Identification of these ‘gatekeeper’ residues and their crucial roles could open up a novel paradigm towards the structure-based design of highly selective pan-inhibitors of oncogenic BCR signaling in the treatment of DLBCL, regardless of signaling dependencies and molecular subtypes.Blocking the oncogenic signaling of B-cell receptor (BCR) has been recently explored as a viable therapeutic approach in the treatment of Diffuse large B-cell lymphoma (DLBCL), an aggressive form of Non-Hodgkin Lymphoma. This involves the multi-targeting of certain members of the SRC kinase family; LYN, FYN and BLK, which propagate BCR signals to downstream effectors. In a recent study, the pharmacological activity of masitinib was repurposed to ‘triple-target’ these SRC kinases. However, it was important to further understand the molecular mechanisms of selectivity and pan-inhibition demonstrated by masitinib to pave way for the design of potent pan-SRC kinase inhibitors. To this effect, we employed molecular dynamics simulation techniques to investigate the interaction dynamics of masitinib towards LYN, FYN and BLK coupled with the molecular basis of selectivity, pan-inhibition and high-affinity binding. Results revealed that, the mechanistic ‘pan-inhibitory’ activities of masitinib towards these SRC kinases entailed the initial selective targeting of catalytic “gatekeeper” residues (Asp334/Glu335 – LYN, Asp130/Asp148/Glu54 – FYN, Asp89 - BLK) and high affinity interactions, which involved strong hydrogen and ionic bonds formation coupled with salt bridges via its (masitinib) piperazine ring at the entrance of the catalytic pockets, followed by systematic access into the deep hydrophobic grooves and eventual disruption of catalytic (kinase) activities. Identification of these ‘gatekeeper’ residues and their crucial roles could open up a novel paradigm towards the structure-based design of highly selective pan-inhibitors of oncogenic BCR signaling in the treatment of DLBCL, regardless of signaling dependencies and molecular subtypes.

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