Comparative Screening and Validation as a Novel Tool to Identify STAT-Specific Inhibitors

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Signal transducers and activators of transcription (STATs) facilitate action of cytokines, growth factors and pathogens. STAT activation is mediated by a highly conserved SH2 domain, which interacts with phosphotyrosine (pTyr) motifs for specific STAT-receptor contacts and STAT dimerization. The active dimers induce gene transcription in the nucleus by binding to specific DNA-response elements of target genes. Abnormal activation of STAT signaling pathways is implicated in many human diseases, like cancer, inflammation and auto-immunity. STAT inhibitory strategies mostly focus on inhibiting STAT dimerization using small molecules identified by molecular modelling, virtual or library screening, or natural products. Searches for STAT-targeting compounds, exploring the pTyr-SH2 interaction area, yielded many small molecules for STAT3 but sparsely for other STATs. So far, no STAT-targeting drug is approved by the FDA. Moreover, many of these inhibitors seem not STAT-specific, thereby questioning the present selection strategies of SH2 domain-based STAT inhibitors. This illustrates the need for better models, and screening and validation tools for more drugable STAT inhibitors with high specificity, potency and excellent bioavailability.

Based on newly developed 3D structure models for all human (h)STATs, we developed a pipeline approach that combines comparative *in silico* docking of STAT-SH2 models with an *in vitro* STAT phosphorylation assay, as a novel tool to screen multi-million compound libraries and identify specific inhibitors for different STATs. Identification of specific and effective STAT inhibitory compounds could provide a tool to increase our understanding of their functional role in different diseases, and serve as therapeutic strategies in cancer, inflammation and auto-immunity.

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