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Repurposing dasatinib for ibrutinib-resistant diffuse large B-Cell lymphoma

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Statement of the problem: Diffuse Large B-Cell Lymphoma (DLBCL) is the most frequent B-cell Non-Hodgkin Lymphoma (B-NHL) which derives from Germinal Center (GC) B cells, and classified into GCB and ABC subtypes, which differ in their cell of origin, genetic alterations and responses to therapy, with ABC having inferior prognosis in response to current immune-chemotherapeutic regimen (R-CHOP). This standard first-line treatment is successful in ~70% of cases by 5-year survival, while the remaining ~30% of patients remains incurable. Bruton Kinase (BTK) inhibitor (Ibrutinib) and PI3K-delta inhibitors are providing novel targeted strategies but their impact on DLBCL is still limited to a fraction of cases, mostly in the ABC subtype.

Methodology & Theoretical Orientation: To identify drugs that can be repositioned for selective efficacy against DLBCL subtypes (GCB- and ABC-DLBCL) compared to non-GC lymphomas, we screened focused libraries including FDA-approved drugs and other promising targeted compounds in advanced clinical testing and the results were validated *in vivo* using DLBCL xenografts.

Findings: Dasatinib has broader activity than Ibrutinib, since it is active against all ABC-DLBCL Ibrutinib-sensitive cell lines along with ABC- and GCB-DLBCL cell lines. Notably, Dasatinib overcomes Ibrutinib-resistance caused by BTK C481S mutation, as Dasatinib is active against ABC-DLBCL lines (LY-10, HBL1 and TMD-8) rendered Ibrutinib-resistant by transduction of BTK C481S mutant. In these cell lines, Dasatinib is unable to suppress BTK-C481S auto-phosphorylation at Tyrosine 223, indicating that Dasatinib may act independently of BTK. As Dasatinib can suppress all three BCR-associated Src-Family Kinases (SFKs) LYN, FYN and BLK, we employed Dasatinib-resistant, gatekeeper mutants of each SFK, alone or in combination, to understand which kinase or combination of kinases needs to be suppressed for Dasatinib activity. Our results showed that FYN suppression is essential for Dasatinib activity in both DLBCL subtypes and PTEN disruption is the most significant predictor of Dasatinib resistance. PTEN is inactivated in most of resistant lines resulting in inability by Dasatinib to restrict PI3K-mediated AKT activation. Furthermore, these data were further validated by showing that 3 Dasatinib-sensitive DLBCL lines were made resistant by transduction of a constitutively active PIK3CA mutant (PIK3CA-H1047R) and the suppression of AKT activation by mTORC2 inhibitors can revert Dasatinib resistance.

Conclusion & Significance: The present study identified the multi-kinase inhibitor Dasatinib as the most DLBCL-specific agent and provided a preclinical framework for Dasatinib-based targeted therapies for DLBCL.

Biography

Sandeep Mittan's overall research goal is to design rational, molecularly-targeted therapies for diffuse large B-cell lymphoma (DLBCL), the most frequent type of B-cell Non-Hodgkin's Lymphoma (B-NHL, 50000 cases/year). To do this, he plans to exploit functional genomics approaches to link DLBCL genetics and epigenetic lesions to pathway sensitivities and therapeutic principles. Ultimately, he wants to build a connectivity map between genetics and drugs, a compass to navigate personalized medicine approaches. We anticipate that our findings will not only identify new drug-gene relationships but also help to address fundamental questions in Germinal Center B-cell biology and shed new light on key pathways in mature B cells.

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