Kinase Inhibitor Screening in Myeloid Malignancies

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KEYWORDS

• Functional screening • Small-molecule inhibitors • Personalized medicine
• Precision medicine • Functional genomics • Chronic neutrophilic leukemia
• Atypical CML

KEY POINTS

- Kinases are common drug targets in myeloid malignancies.
- Kinase dysregulation occurs through a diversity of known and unknown mechanisms.
- Functional screening with kinase inhibitors can foster identification of important kinase targets in myeloid leukemia patient subsets.
- Combining functional screening with genomic data can accelerate understanding of the mechanistic etiology of kinase pathway dependence.

INTRODUCTION

Cancer therapy that is targeted to causative genetic abnormalities has achieved dramatic clinical outcomes in certain malignancy subsets.[1–4] Broad application of this strategy requires a precision medicine approach in which key targets of pathway dysregulation can be rapidly assigned to specific therapeutics in individual patients. The tyrosine kinase gene family, in particular, has played a prominent role as novel targets for cancer therapy over the past several decades.

KINASES AS GENE TARGETS IN MYELOID MALIGNANCY

There are several reasons that kinases and kinase inhibitors have been so broadly explored as cancer therapeutics:

1 Tyrosine kinases play an integral role in numerous cellular processes as diverse as proliferation, apoptosis, differentiation, and cell motililty[5,6]; therefore, dysregulation of tyrosine kinase pathways is likely to contribute to the oncogenic process.
2 There are many examples of specific kinases, both mutated and wild type, that have been directly implicated in the pathogenesis of numerous cancer subsets.[7]

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3 Over the past several decades, a great deal of work has been invested in the development of large arsenals of small molecules that can potently and selectively block the activity of many specific kinases.[7]

Effective translation of this diverse collection of small-molecule kinase inhibitors into a clinical setting requires an understanding of the individual patients and larger patient populations most likely to benefit from different kinase inhibitors. This task is more complex than it might seem, because the routes to kinase pathway dysregulation are numerous and far more complex than a simple genomic lesion in the kinase of interest. Some of these routes are listed as follows, with examples of each taken from the hematologic malignancy literature.

Chromosomal Translocation

Chronic myeloid leukemia (CML) is caused by the 9;22 chromosomal translocation, resulting in the BCR-ABL fusion gene.[8–18] The same BCR-ABL gene fusion has also been implicated in adult and pediatric acute lymphoblastic leukemia (ALL),[19,20] and more recently a wider diversity of tyrosine kinase gene fusions have been reported in ALL cases with similar gene expression signature, but lacking the BCR-ABL–causing chromosomal rearrangement.[21] In addition, there are numerous rearrangements involving fusions of genes in other gene families in hematologic malignancies, and some of these have been reported to lead indirectly to kinase pathway dysregulation.[22–25]

Point Mutations and Insertion/Deletions

One of the best examples of point mutations and insertion/deletions playing a prominent role in hematologic malignancies comes from the myeloproliferative neoplasms, polycythemia vera, primary myelofibrosis, and essential thrombocythemia, in which most cases were found to have point mutations in *JAK2* or *MPL*.[26–34] Subsequently, frameshift mutations in *CALR* were found in most *JAK2*/*MPL* wild-type cases, and these frame-shifted *CALR* mutants were shown to interact with and dysregulate MPL/JAK2 signaling.[35–38] Importantly, this example shows that genetic lesions affecting any number of genes in nonkinase gene families can still lead to kinase pathway dysregulation through complex mechanisms.

Aberrant Expression

Aberrant expression of kinases has been reported in numerous cancers with one of the best-known examples arising from amplification of ERBB2 (HER2) in breast cancer, and examples also exist in hematologic malignancies, such as upregulation of hepatocyte growth factor and its receptor tyrosine kinase, MET, in acute myeloid leukemia (AML).[39]

Oncorequisite Pathways

Although there are numerous examples of a kinase pathway that becomes dysregulated due to a genetic or epigenetic event, there are also emerging examples of pathways that are critical for tumor cell growth and viability without overt alterations in the sequence or expression level of these genes, and specific examples indicate these pathways can be successfully targeted. One of the best examples of this from hematologic malignancies comes from the lymphoid tumors in which the B-cell receptor, which is not mutated and naturally expressed in lymphomas at levels similar to normal B cells, has been demonstrated to be targetable with inhibitors of BCR-associated