The other Achilles' heel of BCR-ABL1

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Inhibition of the BCR-ABL1 tyrosine kinase with selective small molecule tyrosine kinase inhibitors such as imatinib, nilotinib or dasatinib has revolutionized the treatment of chronic myeloid leukemia (CML).[1,2,3] These drugs target the ATP-binding pocket of the ABL1 kinase domain, thereby blocking its kinase activity. While treatment with these inhibitors leads to durable therapeutic responses in chronic phase CML and is superior to previous therapies in advanced CML, the development of resistance, unsatisfactory responses in advanced CML, and problematic long-term tolerance remain major clinical problems. Also, since imatinib, nilotinib and dasatinib target the same ATP-binding pocket in BCR-ABL1, resistance mutations such as the T315I mutation cause resistance to these three drugs. Targeting additional sites on BCR-ABL1 in combination with ATP-competitive inhibitors might result in superior therapeutic responses and could be a way to overcome resistance.

In the past, studies on the structure and dynamics of ABL1/BCR-ABL1 have provided indispensable novel insights in kinase regulatory mechanisms. Binding of the N-terminal myristate moiety to a unique binding pocket in the ABL1 kinase domain was shown to be critical for its autoinhibition.[4] Based on this knowledge, an allosteric myristate-binding pocket inhibitor was developed, which was able to inhibit the pan-resistant BCR-ABL1 T315I mutant when combined with nilotinib.[5]

In a more recent study,[6] the Superti-Furga group elegantly demonstrates the power of structural analysis of ABL1 and BCR-ABL1 kinase regulation to develop new strategies to target BCR-ABL1 activity. Here the authors start from the previous observation that the ABL1 SH2 domain needs to interact with the ABL1 kinase domain for ABL1 activity. The amino acid at position 164 (isoleucine 164) is critical for maintaining this allosteric interaction and mutation of this residue resulted in strongly reduced kinase activity. The research team now demonstrates that also in BCR-ABL1, this intramolecular SH2-kinase domain interaction is necessary for optimal kinase activity. In particular, introduction of an I164E mutation disrupting the interaction resulted in decreased BCR-ABL1 autophosphorylation and *in vitro* kinase activity, decreased downstream activation of STAT5, and, most importantly, completely abolished the capacity of BCR-ABL1 to induce leukemia in mice. Therefore, the SH2-kinase domain interface in BCR-ABL1 represents an attractive drug target in addition to its ATP- and myristate-binding sites. In addition, the authors developed SH2 binding monobodies that sterically hinder the kinase domain to bind to the SH2 domain and as such abolish the critical SH2-kinase interaction. The therapeutic potential of this finding is illustrated by the fact that expression of the monobody in primary CML cells induced apoptosis to a level that was comparable to the effect observed with nilotinib treatment. Despite the fact that intracellular delivery of monobodies will most likely not be possible for therapeutic application, this work nicely validates the SH2-kinase interface as an allosteric target for therapeutic intervention and it might pave the way towards development of cell permeable small molecules that abolish the SH2-kinase interaction in BCR-ABL1.

References

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