Universität Basel

Research Project

Structural and dynamical basis of allosteric regulation and inhibition of abelson tyrosine kinase a drug target in the treatment of chronic mylogeneous leukaemia

Third-party funded project

Project title Structural and dynamical basis of allosteric regulation and inhibition of abelson tyrosine kinase a drug target in the treatment of chronic mylogeneous leukaemia
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Abelson tyrosine kinase (Abl) in its healthy state is a tightly regulated, human protein involved in many cellular processes. An abnormal rearrangement of chromosomes leads to the formation of the aberrant fusion protein Bcr-Abl. Bcr-Abl is highly active and causes uncontrolled production of immature blood cells, which ultimately results in the blood cancers chronic myelogenous leukemia (CML) or acute lymphoblastic leukemia (ALL). Drugs like imatinib (gleevec), nilotinib (tasigna), and dasatinib (sprycel) have been developed to bind to a specific location on Bcr-Abl (ATP-binding pocket) thereby blocking its abnormal activity. They are highly successful in the clinic. However, after prolonged treatment a fraction of the cancers become resistant to these drugs by spontaneous mutations in Bcr-Abl, making the treatment ineffective. Recently, a new class of inhibitors has been discovered that bind to a different location on Bcr-Abl. These so-called allosteric inhibitors have promise to overcome drug resistance in combination with conventional ATP-site inhibitors. The mode of action of this combination is unclear.

Bcr-Abl consists of many subdomains and their relative movement and interplay is thought to be responsible for its regulation. We have recently been able to detect such movements at atomic resolution by Nuclear Magnetic Resonance (NMR) methods. We now want to build on these initial studies and determine Abl's molecular movements and interactions in response to various inhibitors and disease- or functionally relevant mutations by a combination of NMR, single molecule fluorescence resonance energy transfer (FRET) and other biophysical techniques. The results should provide an atomic-level understanding of the mechanism of Abl regulation and a rationale for the improvement of existing and the development of new therapeutic strategies for Bcr-Abl inhibition.

Keywords cancer, abelson kinase, structural biology, nmr
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Published results

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