



ABSTRACT- Steffen Stenger

Abl tyrosine kinase controls phagosomal acidification required for killing of *Mycobacterium tuberculosis* in human macrophages

The mechanisms that regulate the acidification of intracellular compartments are key for host defense against intracellular pathogens. Here we demonstrate that Abl tyrosine kinase, a master switch in cell physiology, controls the acidification of lysosomes. Inhibition of Abl tyrosine kinase by imatinib, a molecular targeted therapy used to treat

chronic leukemia reduced the lysosomal pH in macrophages by increasing the transcription and expression of the vacuolar proton pump vATPase. The acidification was functionally relevant because the activity of cathepsin D and the antimicrobial activity against the major human pathogen *Mycobacterium tuberculosis* were up-regulated in a vATPase dependent manner. These effects could be activated *in vivo* because the frequency of acidic monocytes was higher in the blood of imatinib-treated leukaemia patients than in controls. Given that inhibition of Abl tyrosine kinase enhances the activity of cathepsins and antimycobacterial activity, imatinib or similar antagonists have the potential to complement conventional drug therapy of multidrug- or extremely drug resistant tuberculosis.

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