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Tiivistelmä Referat Abstract

All blood cells are derived from a small number of pluripotent stem cells that are capable of self-renewal and differentiation towards distinct lineage-committed progenitor cells. These committed progenitor cells can undergo proliferation followed by terminal differentiation into mature blood cells that include all the five major groups of hematopoietic cells. The most important hematopoietic growth factor directing the production of granulocytes is granulocyte colony stimulating factor (G-CSF). G-CSF exerts its function by binding to the G-CSF receptor on committed progenitor cells. The majority of hematopoietic cell surface receptors, including the G-CSF receptors lack the ability to phosphorylate protein substrates directly. Instead, ligand induced receptor activation is coupled to downstream signaling events through receptor associated cytoplasmic tyrosine kinases.

In this Pro Gradu thesis, we have studied the role of the Bmx tyrosine kinase, a member of the Tec family of hematopoietically expressed intracellular tyrosine kinases, in the differentiation process of myeloid progenitor cells. The Tec family consists of the founder member Tec, as well as Btk, Itk/Tsk/Emt, Txk and Bmx tyrosine kinases. The proteins of the family share a characteristic domain structure including an amino-terminal pleckstrin homology domain, followed by a Tec homology, src homology 3 and 2 domains and a carboxy-terminal catalytic tyrosine kinase domain. In this study we show that Bmx is catalytically activated by interleukin-3 and G-CSF in 32D myeloid progenitor cells. Activation of Bmx required phosphatidylinositol 3-kinase (PI-3K) as demonstrated by the ability of PI-3K inhibitors to block the activation signal. A green fluorescent protein (GFP) tagged Bmx was translocated to cellular membranes upon co-expression of a constitutively active form of PI-3K, further indicating a role for PI-3K in signaling upstream of Bmx. The expression of wild type Bmx in myeloid progenitor cells resulted in apoptosis in the presence of G-CSF, while cells expressing a kinase dead mutant of Bmx differentiated into mature granulocytes. However, Bmx did not modulate IL-3-dependent proliferation of myeloid progenitor cells. These results demonstrate distinct function for Bmx during cytokine induced proliferation and differentiation of myeloid cells, and suggest that the differentiation stage specific expression of Bmx is critical for successfull myeloid differentiation.

The second goal with this gro gradu thesis was to identify cells outside the hematopoietic system that express Bmx mRNA. By using *in situ* hybridization of embryonic and adult tissue sections, we show that Bmx mRNA is expressed in the endocardium of the heart and in endothelial cells of large arteries. Bmx shows a unique specificity of expression among tyrosine kinase genes and may be involved in signal transduction in these endothelial cells.

Avainsanat Nyckelord Keywords

Bmx gene, tyrosine kinases, signal transduction, endothelial cells, granulocytic differentiation

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