

# Abstract

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## Zinc differentially regulates mitogen-activated protein kinases in human T cells.

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**BACKGROUND:** Zinc is an essential nutrient with remarkable importance for immunity, in particular for T-cell function. This is, at least in part, based on an involvement of zinc ions in immune cell signal transduction; dynamic changes of the intracellular free zinc concentration have recently been recognized as signaling events.

**OBJECTIVE AND METHODS:** Because the molecular targets of zinc signals remain incompletely understood, we investigated the impact of elevated intracellular free zinc on mitogen-activated protein kinase (MAPK) activity and MAPK-dependent cytokine production in human T-cells.

**RESULTS:** p38 was activated by treatment with zinc and the ionophore pyrithione, whereas ERK1/2 and c-Jun N-terminal kinases were unaffected. In contrast, after T-cell receptor stimulation with antibodies against CD3, ERK1/2-phosphorylation was selectively suppressed by intracellular zinc. Mechanisms that had been shown to mediate zinc-effects in other cells, such as activation of the Src kinase Lck, inhibition of the protein tyrosine phosphatase CD45 or MAPK phosphatases and cyclic nucleotide/protein kinase A signaling were not involved. This indicates that the differential impact of zinc on the MAPK families in T-cells is mediated by mechanisms that differ from the ones observed in other cell types. Further investigation of the activation of p38 by zinc demonstrated that this MAPK is responsible for the zinc-mediated activation of CREB and mRNA expression of the Th1 cytokines interferon-gamma and interleukin-2.

**CONCLUSION:** In conclusion, regulation of MAPK activity contributes to the impact of zinc on T-cell function.

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