Intracellular zinc is required for intestinal cell survival signals triggered by the inflammatory cytokine TNFα.


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BACKGROUND: The essential micronutrient zinc has long been known to be a functional component of diverse structural proteins and enzymes. More recently, important roles for free or loosely bound intracellular zinc as a signaling factor have been reported.

OBJECTIVE: Insufficient zinc intake was shown to exacerbate symptoms in mouse models of inflammation such as experimental colitis, while zinc supplementation was found to improve intestinal barrier function. Herein, we provide evidence that intracellular zinc is essential for maintaining intestinal epithelial integrity when cells are exposed to the inflammatory cytokine Tumor Necrosis Factor (TNFα).

METHODS: Using the human intestinal Caco-2/TC7 cell line as an in vitro model, we demonstrate that depletion of intracellular zinc affects TNFα-triggered signaling by shifting intestinal cell fate from survival to death. The mechanism underlying this effect was investigated.

RESULTS: We show that TNFα promotes a zinc-dependent survival pathway that includes modulation of gene expression of transcription factors and signaling proteins. We have identified multiple regulatory steps regulated by zinc availability which include the induction of cellular Inhibitor of APoptosis (cIAP2) mRNA, possibly through activation of Nuclear Factor-Kappa B (NF-κB), as both nuclear translocation of the p65 subunit of NF-κB and up-regulation of cIAP2 mRNA were impaired following zinc depletion. Moreover, X-linked inhibitor of apoptosis protein level was profoundly reduced by zinc depletion.

CONCLUSION: Our results provide a possible molecular explanation for the clinical observation that zinc supplements ameliorate Crohn’s disease symptoms and decrease intestinal permeability in experimental colitis.

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