SL04

Zinc Signaling in Immunity, Inflammation and Allergy

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Zinc (Zn) is an essential nutrient. Zn has been suggested to act as a kind of neurotransmitter. However, it had not been known whether Zn acts as an intracellular signaling molecule, i.e., a molecule whose intracellular status is altered in response to an extracellular stimulus, and that is capable of transducing the extracellular stimulus into an intracellular signaling event. We have proposed that there are at least two kinds of Zn signaling: “late Zn signaling,” which is dependent on a change in the expression profile of Zn transporters, and “early Zn signaling,” which involves a “Zn wave” and is directly induced by an extracellular stimulus (1). 1) We showed that the nuclear localization of Snail is dependent on the Zn transporter, Slc39a6/Zip6/Liv1, a downstream target of STAT3 (2). 2) Slc39a13/Zip13 is involved in TGFb/BMP signaling because of its requirement for the nuclear localization of SMADs. It is required for connective tissue development and a responsible gene of Ehlers-Danlos syndrome (3). 3) Toll-like receptor 4 (TLR4)-mediated dendritic cell maturation is at least in part dependent on a TLR4-induced decrease in intracellular free zinc in a manner dependent on the change of expression profile of zinc transporters (4). 4) FceR1-stimulation induced an increase of intracellular free Zn and we named this phenomenon as "Zn wave" (5). Zn wave seems to originate around ER and it occurs in a several minutes after the stimulation. Thus it is likely that zinc and zinc signaling plays crucial roles in immunity, inflammation and allergy.

1) Hirano et al, Adv. Immunol., 97:149, 2008; 2) Yamashita et al, Nature 429: 298, 2004; 3) Fukada et al, PLoS ONE 3(11):e3642, 2008; 4) Kitamura et al, Nature Immunol.7: 971, 2006; 5) Yamasaki et al, J. Cell Biol. 177: 637, 2007; 6) Nishida et al, J. Exp. Med. 206:1351, 2009