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Elucidation of the Molecular Mechanisms by Which Cells Sence Sodium Environment in the Body via Analyzing Kinases that Bidirectionally and Gradually Respond to Low- and High-Sodium Environment, and their Function in Macrophages

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Summary

Sodium ions (Na^+) are essential for humans. On the other hand, excessive intake of salt has been linked to various diseases. However, molecular mechanisms by which Na^+ affects the body are still not fully understood. In this study, I focused on two kinases, ASK3 and PDK, that we have reported they bidirectionally alter their activity in response to Na^+ environments. I analyzed the molecular mechanisms through which these kinases change their activity depending on Na^+ (osmotic) conditions. In particular, I investigated the liquid–liquid phase separation (LLPS) of ASK3 and the morphological changes of mitochondria. Additionally, since these kinases are expressed in macrophages, I conducted transcriptomic analyses to explore the relationship between Na^+ environment and macrophage functions.

The ASK3 condensates formed by LLPS became smaller and more numerous as extracellular osmolarity increased. The morphological changes increase the condensate surface area led to more efficient dephosphorylation (inactivation) by phosphatases, suggesting that the condensate molphology serves as a quantitative sensor of the Na^+ environment. Furthermore, intracellular Na^+ influx was also necessary for the efficient dephosphorylation of ASK3 through the enhancement of the fluidity of ASK3 condensates.

The super-resolution microscopy analysis revealed that stimulation with high Na^+ led to mitochondrial contraction within seconds and a decrease in membrane potential. At the same time, PDK2 within the mitochondria exhibited a granule-like redistribution. This suggests that activation of PDK, which is involved in mitochondrial metabolic changes, may be induced by the mitochondrial morphological changes.

Peritoneal macrophages from mice were cultured under low, normal, and high Na^+ conditions, and analyzed by RNA-Seq. Many genes responded in opposite directions under low and high Na^+ conditions. Among these, some gene expression changes were lost in ASK3 knockout macrophages. These findings suggest that macrophage are regulated by bidirectionally responsive molecules such as ASK3 and PDK. Elucidating the molecular mechanisms of these Na^+-responsive molecules may lead to a better understanding and potential treatment of Na^+-related diseases involving macrophages.