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Intracellular Ph Modulates Cancer Cell Response to Stress Stimuli

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Dysregulation of intracellular pH (pHi) is one of the hallmarks of cancer cells. Here, we investigated how increased pHi of cancer cells modulates the strength of activation of the c-Jun N-terminal Kinase (JNK) cascade, which mediates cell death in response to stress stimuli. Using quantitative imaging of biosensors for pHi and JNK activity in live cells, we revealed that pHi was an integrated part of the JNK pathway. Changes in pHi defined the strength of the pathway activation in response to various stress stimuli. To understand how pHi modulates the activity of the JNK pathway, we developed optogenetic variants of kinases of the pathway. With this approach, we showed that mild alkalinization of pHi promoted the liquid-liquid phase separation of two pathway kinases, upstream ASK1 and downstream JNK2. Interestingly, the phase transition of ASK1 augmented activation of the JNK pathway, while JNK2 phase separation attenuated JNK activity. Using mathematical modelling, we defined that this differential contribution of JNK2 and ASK1 condensates to JNK pathway activity ensured precise differentiation between stress stimuli in cells. Moreover, our findings suggest that pHi and the ASK1/JNK2 ratio in cells can used to predict cancer cell responses to various anti-cancer drugs.