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Research on DNA Damage Induction by Salt, Cell Response Mechanism, and Its Involvement in Carcinogenesis

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Summary

Replication stress, a hallmark of cancer, can be triggered by oncogenes and various biological stresses like heat, osmotic stress, oxidative stress, and hypoxia. These stresses activate Chk1, a crucial kinase in the replication checkpoint, through Claspin.

Claspin, known for regulating DNA replication, plays a novel role in cellular stress responses. It mediates Chk1 activation in response to various stresses, some of which directly inhibit DNA replication while others activate Chk1 through replication-independent mechanisms.

The activation of Chk1 during S phase, when DNA replication occurs, is Claspin-dependent, while activation in G1 phase is mostly independent of Claspin. This suggests that Claspin primarily acts as a mediator in the DNA replication-related Chk1 activation pathway.

Interestingly, heat stress induces hyperphosphorylation of Claspin. Experiments with cells deficient in eIF2α kinases (PERK, GCN2, PKR, and HRI) showed that GCN2 and HRI are required for Claspin-Chk1 activation and the cellular heat stress response.

Mass spectrometry identified five phosphorylation sites at the C-terminus of Claspin that are phosphorylated under heat stress. Biochemical analysis confirmed that GCN2 and HRI are responsible for this phosphorylation.

Furthermore, mutant cell lines lacking these phosphorylation sites were unable to activate the checkpoint or stop DNA replication under heat stress. These cells experienced high DNA damage and low viability, highlighting the importance of eIF2a kinase-mediated Claspin phosphorylation in cellular survival under heat stress.

In conclusion, this study reveals new connections between the replication stress checkpoint and various biological stresses. It also uncovers Claspin's multifaceted roles, highlighting its involvement in both DNA replication and stress response pathways. The findings provide insights into the complex mechanisms of Chk1 activation and cellular response to stress, with potential implications for cancer research and therapy development.