Online links

URLs
Entrez genome:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=genome
KSHV
http://www.ncbi.nlm.nih.gov/genomes/framik.cgi?db=genome&gi=15951

VIRAL PATHOGENESIS

Preserving the message

A new report in *Science* has shed light on the mechanism that leads to the overproduction of cytokines by cells that are infected with Kaposi's sarcoma-associated herpesvirus (KSHV). KSHV is aetiologically linked to Kaposi's sarcoma and other rare lymphoproliferative diseases, and elevated levels of proinflammatory cytokines are a characteristic and pathologically relevant feature of these disorders.

Craig McCormick and Don Ganem suspected that kaposin B — a KSHV protein that is expressed by latently infected cells — might be implicated in this dysregulated inflammatory response. By using kaposin B as bait in a yeast two-hybrid screen, the authors showed that the mitogen-activated protein kinase (MAPK)-associated protein kinase-2 (MK2) interacted with this viral protein.

Interestingly, kaposin B co-localized with GFP-tagged MK2 in the nucleus of human cells, and both MK2 and kaposin B relocated from the nucleus to the cytoplasm when the cells were exposed to inflammatory stress. Also, the co-expression of MK2 and kaposin B resulted in the increased phosphorylation of MK2 and its substrate heat-shock protein-27 (HSP27), which suggested to the authors that this interaction was functionally significant.

So how does the kaposin-B–MK2 complex affect cytokine production? Cytokine transcripts are enriched in 3′ AU-rich elements (AREs) that destabilize the mRNA, causing its rapid degradation. It is well known that elevated MK2-kinase activity counteracts the destabilizing effect of the AREs, and so the kaposin-B–MK2 complex might act at the level of cytokine mRNA. This proved to be the case: McCormick and Ganem showed that, *in vitro*, kaposin B — but not other latent viral proteins — stabilized transcripts that contain AREs. Importantly, in cells with latent KSHV infection, the half-life of ARE-containing transcripts was prolonged, and the levels of cytokines GM-CSF and IL6 were markedly elevated.

It is still not known exactly how kaposin B activates MK2. The viral protein might interact with p38MAPK — an upstream activator of MK2 that immunoprecipitates with the kaposin-B–MK2 complex. It is more likely, however, that the kaposin-B–MK2 interaction somehow stabilizes MK2, facilitating the efficient phosphorylation of MK2 by p38MAPK in the nucleus. Phosphorylated MK2 then activates target proteins, which block the degradation of ARE-containing cytokine transcripts. The signalling molecule MKK6 — a component of the p38/MK2 pathway — also contains an ARE in its mRNA, and the authors propose that the consequent increased levels of MKK6 might function in a positive-feedback loop.

Shannon Amoils

References and links

ORIGINAL RESEARCH PAPER McCormick, C. & Ganem, D. The kaposin B protein of KSHV activates the p38/MK2 pathway and stabilizes cytokine mRNAs. *Science* **307**, 739–741 (2005)

WEB SITE

Don Ganem's laboratory:
http://itsa.ucsf.edu/~micro/Faculty/ganem_folder/index.html