nature research

https://doi.org/10.1038/s41580-020-00322-w

Supplementary information

Diversity and versatility of p38 kinase signalling in health and disease

In the format provided by the authors and unedited

Supplementary BOX 1: Overview of the cellular stress response

"Stress response" is a broad term that could be defined as the network of mechanisms that sense and signal any alteration in the cellular homeostasis to facilitate the appropriate biological outcome. It seems likely that every cell in an organism is subjected to different kind of stresses during its lifetime, both in homeostatic and pathological conditions. Since most extracellular or intracellular imbalances can be sensed as a potential risk, cells can engage several molecular mechanisms depending on the nature, strength, and duration of the stress, as well as on the cellular context. Coordination of these mechanisms is essential for achieving an adequate response at the cellular level, which also impacts on tissue and organism homeostasis [1]. Although transcriptional and translational reprogramming, mRNA splicing or protein stability are all known to participate in the stress response [2-6], protein phosphorylation is perhaps the most rapid and effective mechanism for a cell to react to an unexpected threat. Therefore, it is rather common to find protein kinases as sensors and/or drivers of the stress response. The specificity is achieved, at least in part, by the specialization of particular kinases that react to certain stresses. Thus, DNA damage engages ATM and ATR [7], endoplasmic reticulum stress leads to PERK activation [8], AMPK is a sensor of energy depletion [9], PKR responds to viral infections, and GCN2 is activated following amino acid deprivation [10]. In contrast, the MAPKs of the JNK and p38 subfamilies have been implicated in multiple stress responses. In particular, p38 kinases play key roles in oxidative and osmotic stress or inflammation, but also contribute to the regulation of the response to many other stresses by serving as mediators or modulators of various signalling pathways, emerging as crucial coordinators of the stress response.

1 Galluzzi, L., Yamazaki, T. & Kroemer, G. Linking cellular stress responses to systemic homeostasis. *Nat Rev Mol Cell Biol* **19**, 731-745 (2018).

2 Flick, K. & Kaiser, P. Protein degradation and the stress response. *Semin Cell Dev Biol* **23**, 515-522 (2012).

3 Kucherenko, M. M. & Shcherbata, H. R. miRNA targeting and alternative splicing in the stress response - events hosted by membrane-less compartments. *J Cell Sci* **131**, jcs202002 (2018).

4 de Nadal, E. & Posas, F. Osmostress-induced gene expression - a model to understand how stress-activated protein kinases (SAPKs) regulate transcription. *FEBS J* **282**, 3275-3285 (2015).

5 Vihervaara, A., Duarte, F. M. & Lis, J. T. Molecular mechanisms driving transcriptional stress responses. *Nat Rev Genet* **19**, 385-397 (2018).

6 Himanen, S. V. & Sistonen, L. New insights into transcriptional reprogramming during cellular stress. *J Cell Sci* **132**, jcs238402 (2019).

7 Blackford, A. N. & Jackson, S. P. ATM, ATR, and DNA-PK: The Trinity at the Heart of the DNA Damage Response. *Mol Cell* **66**, 801-817 (2017).

8 Hetz, C., Zhang, K. & Kaufman, R. J. Mechanisms, regulation and functions of the unfolded protein response. *Nat Rev Mol Cell Biol* **21**, 421-438 (2020).
9 Herzig, S. & Shaw, R. J. AMPK: guardian of metabolism and mitochondrial homeostasis. *Nat Rev Mol Cell Biol* **19**, 121-135 (2018).
10 Pakos-Zebrucka, K. *et al.* The integrated stress response. *EMBO Rep* **17**, 1374-1395 (2016).