Nature Reviews Molecular Cell Biology | Published online 5 Apr 2017

IN BRIEF

CELL SENESCENCE

A new role for ATM

Cell senescence is associated with permanent withdrawal from the cell cycle in response to various stresses and ageing. Kang *et al.* screened human fibroblasts for factors that alleviate senescence and identified the major DNA damage repair kinase ATM as one of the hits. ATM interacted with the subunits of the lysosomal proton pump, and by phosphorylating them prevented the functional association of the subunits. This led to an increase in lysosomal pH and interfered with the removal of dysfunctional mitochondria by autophagy. As a consequence, cells accumulated defective mitochondria, which resulted in metabolic dysfunction and senescence. Inhibition of ATM reversed these negative effects and prevented senescence. Thus, ATM promotes cell senescence, suggesting that controlled inhibition of ATM could potentially counteract senescence and ageing.

ORIGINAL ARTICLE Kang, H. T. *et al.* Chemical screening identifies ATM as a target for alleviating senescence. *Nat. Chem. Biol.* http://dx.doi.org/10.1038/nchembio.2342 (2017)

DNA DAMAGE RESPONSE

RNA m^{6}A regulates DNA repair

Xiang *et al.* screened human cell lines for chromatin-associated factors that participate in the DNA damage response. Ultraviolet (UV) irradiation caused rapid and transient methylation at the 6 position of adenosine (m^{6}A), predominantly in 5′ untranslated regions of poly(A)$^+$ RNA, including in transcripts localized at sites of DNA damage. RNA methylation was carried out by the methyltransferase METTL3 together with its cofactor METTL14, and was subsequently removed by the demethylase FTO; methylation was also dependent on PARP, which possibly recruits METTL3 to damage sites. Accumulation of m^{6}A following UV irradiation was required for transcription re-initiation and for cell survival, through the recruitment of the repair and translesion synthesis DNA polymerase Pol κ to damage sites. Importantly, METTL3-depleted cells exhibited repair defects, which were rescued by Pol κ overexpression. Together, PARP, METTL3, m^{6}A RNA and Pol κ might constitute a new, UV-induced DNA damage repair pathway.

ORIGINAL ARTICLE Xiang, Y. *et al.* RNA m^{6}A methylation regulates the ultraviolet-induced DNA damage response. *Nature* **543**, 573–576 (2017)

LIPID METABOLISM

Cholesterol feeds into cell growth control

mTORC1 is a master regulator of cell growth, which responds to nutrient availability — in particular, amino acids. Castellano *et al.* now show that mTORC1 is also regulated by cholesterol, suggesting a strong link between sterol metabolism and cell growth control. Cholesterol is metabolized in the lysosome, which is also the site of mTORC1 activation, owing to the tethering of RAG GTPases, which regulate mTORC1 activity, to lysosomes. The authors found that an increase in lysosomal cholesterol level stimulated mTORC1 signalling, whereas cholesterol depletion suppressed it. The lysosomal amino acid transporter SLC38A9 was then found to also bind to cholesterol and to translate high cholesterol levels to mTORC1 activation through the regulation of RAG GTPase activity. Finally, the cholesterol-mediated mTORC1 activation was demonstrated to be negatively regulated by the cholesterol transporter NPC1, which is involved in cholesterol export from lysosomes.

ORIGINAL ARTICLE Castellano, B. M. *et al.* Lysosomal cholesterol activates mTORC1 via an SLC38A9-Niemann–Pick C1 signaling complex. *Science* **355**, 1306–1311 (2017)