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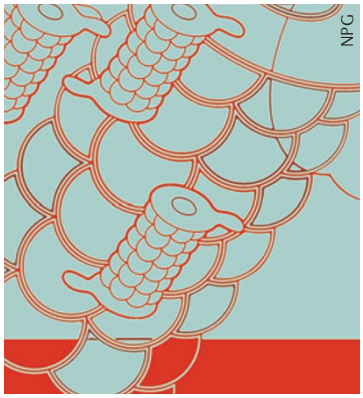

Targeting tumour-supportive cellular machineries p179

The p53 pathway as a drug target p217

Although the endogenous ligands for many nuclear receptors remain unidentified, those for REV-ERB and the retinoic acid receptor-related orphan receptors (RORs) have recently been found. Burris and Kojetin review the roles of these receptors in diseases ranging from arthritis to cancer, and describe the substantial efforts that have been made to develop synthetic ligands as potential drugs. Two further articles in this month's issue are on cancer. In their Perspective, Dobbelstein and Moll view the historical development of anticancer drugs in three 'waves': a first wave of drugs targeting DNA replication and cell division; a second wave targeting tumour-specific signalling intermediates; and a third wave targeting multimolecular complexes involved in processes such as chromatin modification, protein folding and protein turnover. Focusing on the third wave of drugs, which are currently being intensely investigated, they discuss the potential of these agents to address the limitations of drugs from the first two waves, as well as opportunities for the development of combination therapies based on drugs from different waves. Finally, Lane and colleagues review progress with anticancer strategies based on restoring or activating the function of p53, a transcription factor with tumour-suppressive activity that is compromised in many cancers. Various agents are now in clinical trials — in particular, small molecules that prevent the interaction of p53 with its negative regulators, MDM2 and MDMX — and the authors also discuss issues that will be important in realizing their potential, such as the identification of appropriate tumour types and the selection of other components of potential combination therapies.

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