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ANTICANCER AGENTS

Digging in

There are many essential processes that are carried out in a cell, and some of these rely on the cofactor NAD^+. Javed Khan and colleagues have identified a means of specifically inhibiting NAD^+ production, a process known to induce tumour cell death.

Many of the biochemical processes that require NAD^+, such as the repair of DNA strand breaks involving the enzyme poly (ADP-ribose) polymerase, lead to a decrease of NAD^+ molecules. These are replenished by a salvage pathway that involves the enzyme nicotinamide phosphoribosyltransferase (NMPRTase). Inhibitors of NMPRTase have been known for some time, but it has not been clear how they function. So Khan and colleagues crystallized mouse and human NMPRTase with substrate, with an inhibitor and with neither, and solved their structures.

They found that NMPRTase is a dimer, and that there is a 'tunnel' at the interface between the two monomers, with the active site at one end of the tunnel. The co-crystal structure of NMPRTase with the inhibitor FK866 showed that FK866 binds tightly within the tunnel and prevents access to the active site. The shape of the tunnel restrains the types of chemicals, and therefore inhibitors, that can bind, and the presence of the tunnel in the NMPRTase, but not the related enzymes NAPRTase or QAPRTase, should ensure specificity.

FK866 will induce apoptosis in tumour cells that have increased levels of NMPRTase activity, which indicates that NMPRTase is a target worth pursuing for cancer therapy.

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URLs

ORIGINAL RESEARCH PAPER Khan, J.A., Tao, X. & Tong, L. Molecular basis for the inhibition of human NMPRTase, a novel target for anticancer agents. *Nature Struct. Mol. Biol.* **13**, 582–588 (2006)