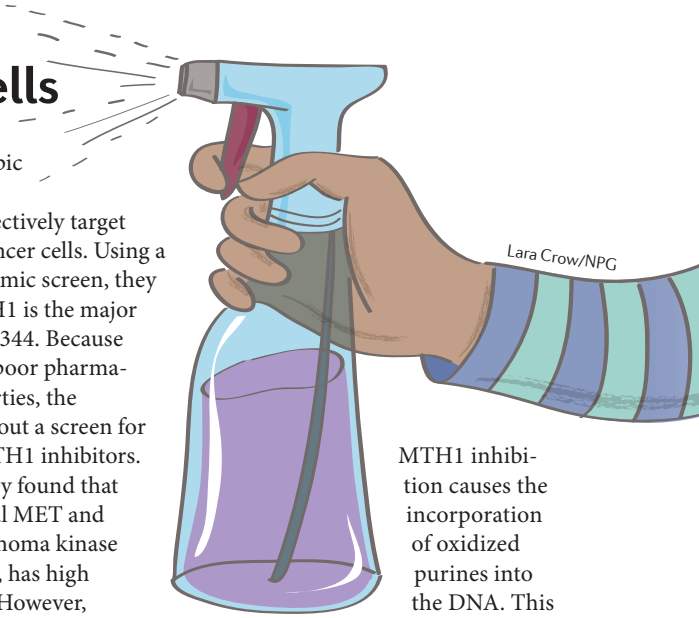
Nature Reviews Cancer | AOP, published online 17 April 2014; doi:10.1038/nrc3734

DNA DAMAGE

De-sanitizing tumour cells



MTH1 is a 'sanitizing' enzyme that catalyses the hydrolysis of oxidized purine nucleotides, which stops potentially mutagenic triphosphates, such as 8-oxo-2′-deoxyguanosine (8-oxo-dG) and 2-hydroxy-2′-deoxyadenosine (2-OH-dA), from being incorporated into DNA. Two papers now report that inhibition of MTH1 is lethal to tumour cells with high levels of oxidative damage.

Helleday and colleagues showed that knockdown of MTH1 reduced the survival of several cancer cell lines but not of VH10 primary fibroblasts (which have lower levels of reactive oxygen species). MTH1 knockdown increased the levels of 8-oxo-dG and 2-OH-dA in DNA and induced markers of DNA double-strand break repair, irrespective of p53 expression. Moreover, the survival of mice was improved when MTH1 knockdown was induced in SW480 colorectal adenocarcinoma cell xenograft tumours, thereby establishing MTH1 as a promising anticancer target.

Next, the authors undertook a compound screen for MTH1 inhibitors and went on to develop TH287 and TH588. Both drugs were toxic to several cancer cell lines but did not induce cell-killing of normal and immortalized cell lines. Interestingly, varying levels of the base excision repair (BER) glycosylases that initiate DNA repair of 8-oxo-dG and 2-OH-dA did not affect the toxicity of the drugs, nor did the expression of p53. In addition, using a patient-derived xenograft, the authors found that tumour growth was reduced after treatment with TH588.

Superti-Furga and colleagues took a different approach. The compound SCH51344 was identified from a phenotypic screen of compounds that selectively target RAS-mutant cancer cells. Using a chemical proteomic screen, they found that MTH1 is the major target of SCH51344. Because SCH51344 has poor pharmacological properties, the authors carried out a screen for more potent MTH1 inhibitors. Remarkably, they found that crizotinib, a dual MET and anaplastic lymphoma kinase (ALK) inhibitor, has high MTH1 affinity. However, further investigation revealed that crizotinib is a chiral compound and the (*S*)-enantiomer has potent (nanomolar) half-maximal inhibitory concentration (IC_{50}) values for MTH1; (*R*)-crizotinib had IC_{50} values in the micromolar range. Conversely, (*R*)-crizotinib had more potent activity towards ALK and MET than (*S*)-crizotinib.

(*S*)-crizotinib inhibited colony formation of SW480 and PANC1 human pancreatic carcinoma cells and induced markers of activated DNA damage responses. Moreover, the authors found that SCH51344 and (*S*)-crizotinib induced a significant level of DNA breakage, whereas (*R*)-crizotinib did not. The level of DNA damage was increased further by the addition of purified DNA glycosylases that initiate BER of 8-oxo-dG and 2-OH-dA. Importantly, they also showed that cell death induced by MTH1 inhibition is independent of the expression or activity of several DNA damage response proteins, including p53, ataxia-telangiectasia and RAD3-related (ATR) and ataxia-telangiectasia mutated (ATM). Together, this indicates that MTH1 inhibition causes the incorporation of oxidized purines into the DNA. This activates BER, which probably becomes saturated, leading to DNA breakage at repair intermediates and loss of cell viability. Furthermore, the authors showed that (*S*)-crizotinib — but not (*R*)-crizotinib — reduced the progression and volume of SW480 xenograft tumours *in vivo*.

Some of the most commonly used chemotherapies have a broad application because they target a common phenotype that has some specificity to cancer cells, such as hyperproliferation. It could be that the commonality of substantially increased oxidative damage in cancer cells means that targeting MTH1, and possibly other enzymes with similar functions, may also be a broadly effective anticancer strategy. However, further investigation into how general this approach can be, especially *in vivo*, is important.

Gemma K. Alderton

> “inhibition of MTH1 is lethal to tumour cells with high levels of oxidative damage”

ORIGINAL RESEARCH PAPERS Huber, K. V. M. *et al.* Stereospecific targeting of MTH1 by (*S*)-crizotinib as an anticancer strategy. *Nature* http://dx.doi.org/10.1038/nature13194 (2014) | Gad, H. *et al.* MTH1 inhibition eradicates cancer by preventing sanitation of the dNTP pool. *Nature* http://dx.doi.org/10.1038/nature13181 (2014)