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GENETICS

Common co-deletion isn't a silent passenger

> *MTAP* loss renders cells sensitive to inhibition of protein arginine methyltransferase 5

Methylthioadenosine phosphorylase (MTAP) is a ubiquitously expressed enzyme involved in the methionine salvage pathway. Homozygous deletion of *MTAP* is frequently seen in many human tumours, as the gene is located near to *CDKN2A* (which encodes cyclin-dependent kinase inhibitor 2A). Two studies in *Science* report that *MTAP* loss renders cells sensitive to inhibition of protein arginine methyltransferase 5 (PRMT5), a dependency that could be therapeutically targeted in *MTAP*-deleted cancers.

Kryukov *et al.* and Mavrakis *et al.* carried out large-scale short-hairpin RNA (shRNA)-mediated screens across cell lines from a range of cancer types to identify genes required for viability in *MTAP*-null but not *MTAP*-sufficient cells. For both groups, *PRMT5* was the most significant hit.

Confirming that PRMT5 dependence is specifically induced by *MTAP* loss, cancer cell lines lacking *MTAP* or both *CDKN2A* and *MTAP* were shown to be sensitive to *PRMT5* knockdown, whereas those lacking only *CDKN2A* were not (Mavrakis *et al.*). Furthermore, sensitivity to *PRMT5* knockdown was reduced by transducing four different *MTAP*-null cancer cell lines with *MTAP* (Kryukov *et al.*) and, conversely, was induced by CRISPR-mediated *MTAP* knockout in an *MTAP*-sufficient cancer cell line (Mavrakis *et al.*). PRMT5 activity was required for the effects of *MTAP* loss on cell viability, as the expression of catalytically inactive mutants of PRMT5 did not rescue the growth of *MTAP*-null cells in which *PRMT5* was knocked down. In addition, using xenograft models of established disease induced by subcutaneous injection of mice with *MTAP*-null or *MTAP*-sufficient cancer cell lines engineered to inducibly express *PRMT5*-specific shRNAs, Mavrakis *et al.* demonstrated that *in vivo PRMT5* knockdown markedly reduced tumour volume only in mice with *MTAP*-null tumours.

What mechanism links *MTAP* loss to PRMT5 dependence? Both groups investigated the role of methylthioadenosine (MTA), the substrate of MTAP, which had previously been suggested as a pan-PRMT inhibitor. Consistent with published data from studies analysing *MTAP*-deleted tumours, both groups found markedly increased levels of intracellular MTA in *MTAP*-null cell lines from various cancer types, a phenotype that was reversed by re-expression of *MTAP*. In addition, MTA levels were increased by CRISPR-mediated *MTAP* knockout in an *MTAP*-sufficient cancer cell line (Mavrakis *et al.*).

In line with the hypothesized role of MTA as a pan-PRMT inhibitor, increased intracellular MTA levels correlated with reduced catalytic activity of PRMT5 in *MTAP*-null cell lines (both groups). This correlation was not observed in isogenic *MTAP*-reconstituted cell lines (both groups) but was observed in *MTAP*-sufficient cell lines treated with exogenous MTA (Kryukov *et al.*). Both groups used different assays to profile the ability of MTA to inhibit the catalytic activity of a panel of methyltransferases and showed that rather than being a pan-PRMT inhibitor, MTA is selective for PRMT5, and acts through a mechanism distinct from that of the PRMT5-selective inhibitor EPZ015666. Further characterizing the PRMT5 selectivity of MTA, crystal structure analyses revealed the key PRMT5 residues responsible for the conformational change induced by MTA binding (Mavrakis *et al.*).

These studies show that in the setting of *MTAP* loss, increased levels of MTA inhibit PRMT5 and render cancer cells sensitive to further PRMT5 inhibition. Thus, targeted therapies that exploit this vulnerability could be used to treat tumours in which *MTAP* is co-deleted with *CDKN2A*.

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ORIGINAL ARTICLES Kryukov, G. V. *et al.* *MTAP* deletion confers enhanced dependency on the PRMT5 arginine methyltransferase in cancer cells. *Science* http://dx.doi.org/10.1126/science.aad5214 (2016) | Mavrakis, K. J. *et al.* Disordered methionine metabolism in MTAP/CDKN2A deleted cancers leads to dependence on PRMT5. *Science* http://dx.doi.org/10.1126/science.aad5944 (2016)

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