BIOBUSINESS BRIEFS

TARGET WATCH

PKMYT1: a forgotten member of the WEE1 family

WEE1, the founding member of the WEE kinase family, has been implicated in over a dozen cancer types. This has led to extensive efforts to develop inhibitors; for example, adavosertib (AZD1775), a leading selective WEE1 inhibitor, has been tested as a single agent and in combination in more than 50 clinical trials in patients with cancer. So far, however, another member of the family, PKMYT1 has been largely ignored, although it shares a high degree of functional redundancy with WEE1 and so could also represent a promising and tractable target.

Biological functions

Functionally, both WEE1 and PKMYT1 phosphorylate cyclin-dependent kinase 1 (CDK1) to inhibit its activity and prevent association with cyclin B. CDK1 is a master regulator of the cell cycle, activation of which is essential for entry into mitosis, meaning that PKMYT1 and WEE1 might be expected to act as tumour suppressors by preventing CDK1 activation. However, studies show that loss of either kinase interferes with the G2–M checkpoint, driving cells into mitosis prematurely (*Oncogene* **32**, 4778–4788; 2013). Unchecked mitotic entry results in the accumulation of genetic lesions from unrepaired DNA damage, ultimately leading to apoptosis or mitotic catastrophe. Thus, treatment strategies targeting WEE1 have largely focused on inhibitors in combinations with chemotherapies and radiotherapy, which cause DNA damage.

Inhibitor development and functional characterization of PKMYT1 has severely lagged behind WEE1, despite their seemingly redundant functions in the regulation of CDK1. In genome-wide CRISPR screens of 563 cell lines, both WEE1 and PKMYT1 were found to be essential in almost all cell lines tested (see Related links), suggesting that loss of either kinase is sufficient to inhibit growth of cancer cells. PKMYT1 has also been implicated in an increasing number of cancer types, including gastric cancer, non-small-cell lung cancer, hepatocellular carcinoma, glioblastoma, neuroblastoma and colorectal cancer, in which overexpression of PKMYT1 generally correlates with poor prognosis and disease progression. There is also a notable difference in the functions of PKMYT1 versus WEE1. WEE1 has only been shown to phosphorylate CDK1 at Thr14, whereas PKMYT1 has dual activity for Thr14 and Tyr15 (*Science* **270**, 86–90; 1995). In addition, WEE1 primarily localizes to the nucleus, whereas PKMYT1 is predominantly cytosolic and associates with the Golgi apparatus and endoplasmic reticulum through a membrane tether. Through its extranuclear localization, PKMYT1 further regulates CDK1 by sequestering it in the cytosol. PKMYT1 also has another key role in the cell cycle — regulating Golgi membrane reassembly following mitosis — and depletion of PKMYT1 leads to cell death (*J. Cell Biol.* **181**, 89–103; 2008).

Chemical tools

Broad kinome screening has shown that small molecules can bind to PKMYT1, but these data have not yet led to a suitable chemical probe to study PKMYT1 biology, as most compounds in the literature are broad-spectrum kinase inhibitors that lack specificity and potency for this target. However, there are several chemotypes that have promise as effective starting points, such as dianilinopryimidines; one example has an IC_{50} of 500 nM for PKMYT1, although the broader kinome selectivity profile is unknown (*Eur. J. Med. Chem.* **161**, 479–492; 2019). A number of examples of the oxindole chemotype also look encouraging, with relatively narrow-spectrum kinome profiles and potency in a microfluidics capillary electrophoresis assay, which highlighted compound GW406108X (*Nat. Biotechnol.* **34**, 95–103; 2016). Several examples of kinase inhibitors have also recently been co-crystallized with PKMYT1 and other WEE1 family members (FIG. 1). These crystal structures provide valuable insight into the design of chemical probes and potential therapeutics for this emerging, potentially clinically important kinase.

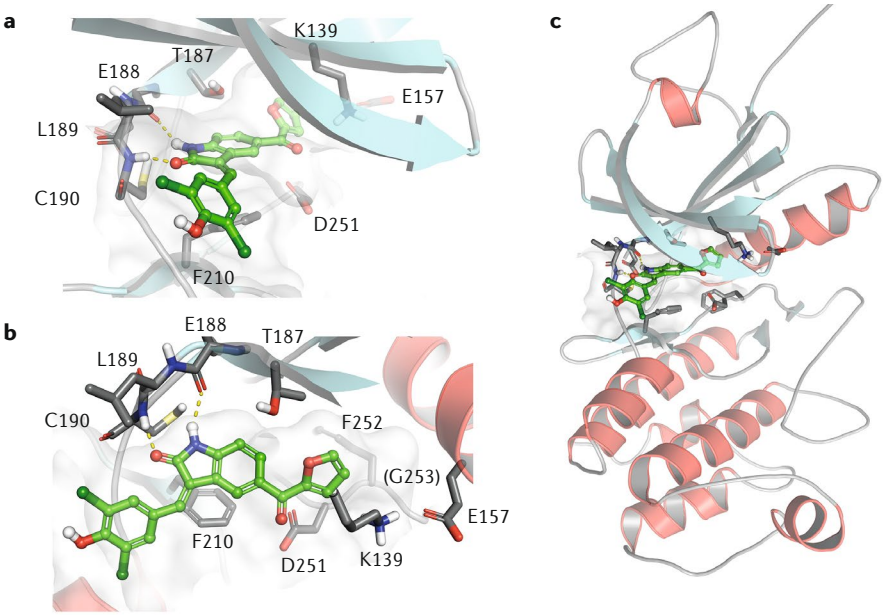

Fig. 1 | **PKMYT1 structure and inhibitor docking.** The figure shows the oxindole inhibitor GW406108X docked into the structure of PKMYT1, obtained in complex with dasatinib (PDB ID: 5VCV). **a** | The solvent-exposed cavity. **b** | Hinge region. **c** | Wider view of the whole complex.

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https://doi.org/10.1038/d41573-019-00202-9

Acknowledgements
This article is part of a series from the NIH Common Fund Illuminating the Druggable Genome (IDG) program. The goal of IDG is to catalyse research on understudied proteins from druggable gene families by providing reagents, phenotypes and a mineable database, focusing on GPCRs, kinases and ion channels.

Competing interests
The authors declare no competing interests.

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