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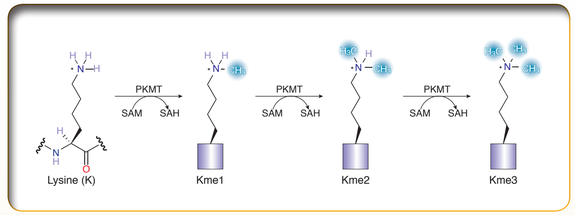
The human protein methyltransferases

Methyltransferases are enzymes that facilitate the transfer of a methyl ($-CH_3$) group to specific nucleophilic sites on proteins, nucleic acids or other biomolecules. They share a reaction mechanism in which the nucleophilic acceptor site attacks the electrophilic carbon of *S*-adenosyl-L-methionine (SAM) in an S_N2 displacement reaction that produces a methylated biomolecule and *S*-adenosyl-L-homocysteine (SAH) as a byproduct. Methylation reactions are essential transformations in small-molecule metabolism, and methylation is a common modification of DNA and RNA. The recent discovery of dynamic and reversible methylation of amino acid side chains of chromatin proteins, particularly within the N-terminal tail of histone proteins, has revealed the importance of methyl 'marks' as regulators of gene expression. Human protein methyltransferases (PMTs) fall into two major families—protein lysine methyltransferases (PKMTs) and protein arginine methyltransferases (PRMTs)—that are distinguishable by the amino acid that accepts the methyl group and by the conserved sequences of their respective catalytic domains. Given their involvement in many cellular processes, PMTs have attracted attention as potential drug targets, spurring the search for small-molecule PMT inhibitors. Several classes of inhibitors have been identified, but new specific chemical probes that are active in cells will be required to elucidate the biological roles of PMTs and serve as potent leads for PMT-focused drug development.

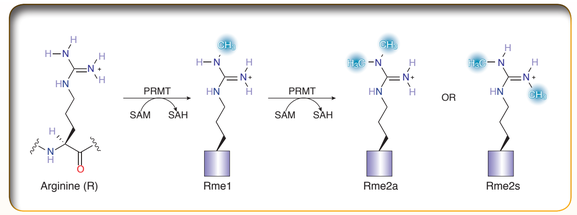
Protein lysine methyltransferases (PKMTs)

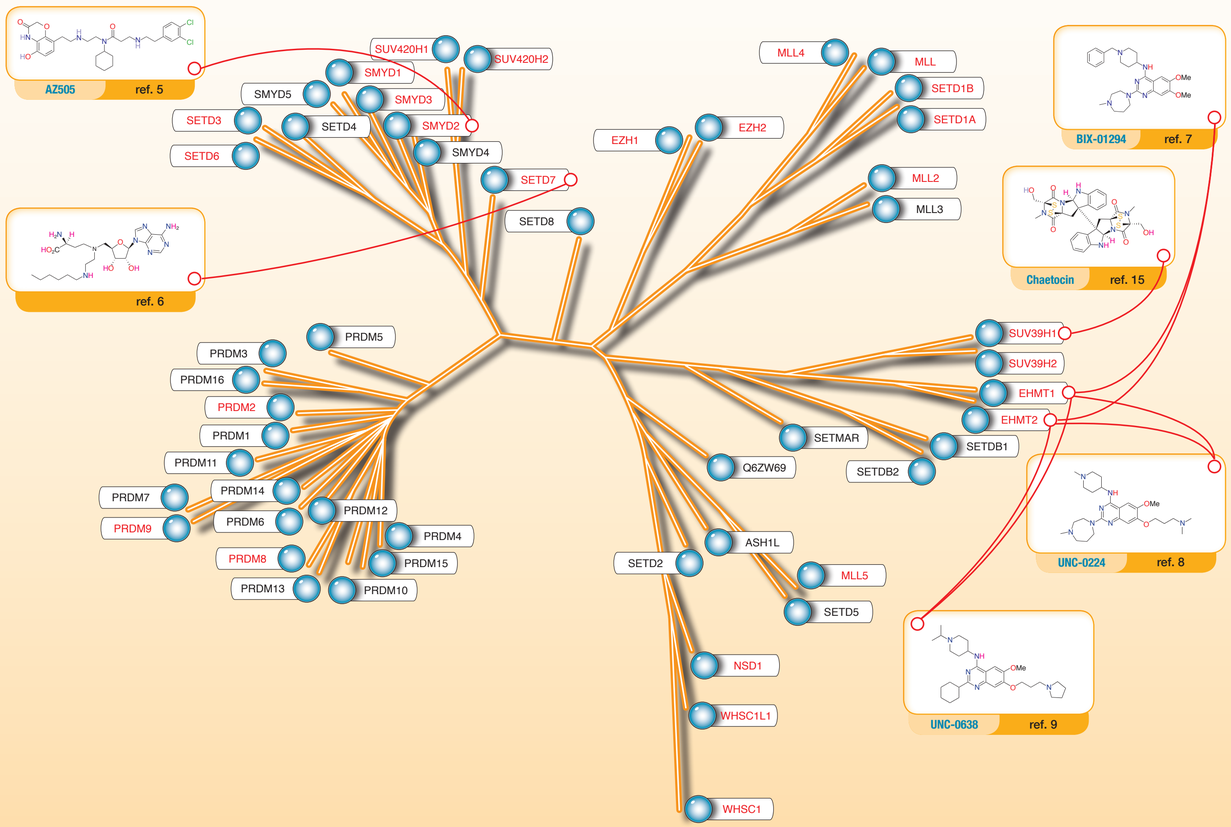
The phylogenetic tree shows 51 genes predicted to encode PKMTs, which are positioned in the tree on the basis of the similarities of their amino acid sequences[1]. This tree excludes one validated PKMT, DOT1L, which lacks a SET domain—the catalytic domain conserved in this family—and clusters more closely with the PRMTs. The tree has four major branches, and each branch contains enzymes with validated methyltransferase activity (highlighted in red). Some PKMTs add a single methyl group, resulting in a monomethylated product (Kme), whereas others produce di- (Kme2) or trimethylated (Kme3) lysine modifications. Many of the validated PKMTs methylate lysines on histones, though nonhistone substrates have also been identified.

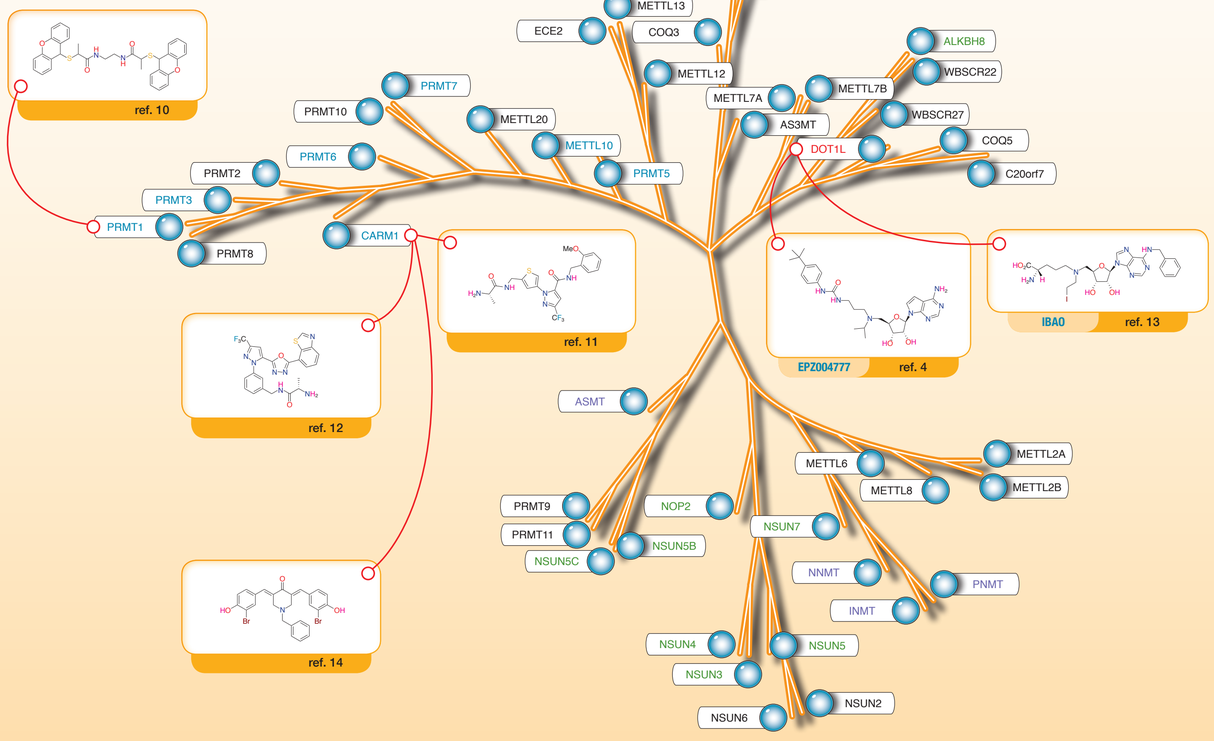


Protein arginine methyltransferases (PRMTs)

The human PRMT phylogenetic tree comprises 45 predicted enzymes including the PKMT DOT1L[1]. There are two major types of PRMT; both catalyze the formation of monomethylarginine (Rme1) but distinct reaction mechanisms yield symmetric (Rme2s) or asymmetric (Rme2a) dimethylarginine. A small number of predicted PRMTs have validated activity (highlighted in blue). In addition to PRMTs, this tree includes validated RNA methyltransferases (highlighted in green) and biosynthetic enzymes (highlighted in violet). It remains uncertain whether these latter enzymes have PRMT activity, despite their shared structural features. Substrates for the enzymes shown include RNA, metabolites, histones and RNA-binding and spliceosomal proteins.







Targeting PMTs

- A selection of small-molecule PMT inhibitors with some target selectivity is shown (minimally validated in quantitative *in vitro* assays) around the trees along with the name of the molecule, citation information and the chemical structure[2,3].
- DOT1L is a validated therapeutic target for mixed-lineage leukemia[4]. The majority of these leukemias result from chromosomal rearrangements that cause aberrant recruitment of DOT1L to MLL-fusion target genes. Inhibition of DOT1L with EPZ004777 demonstrated that these leukemia cells are addicted to DOT1L activity and established proof of concept for DOT1L inhibition as a therapeutic option.
- Priority therapeutic targets also include MLL for leukemias; SETD1B and CARM1 for neurodegeneration; as well as EZH2, SMYD3 and EHMTs for multiple cancers.
- Additional PMTs have been implicated in human diseases and may yet emerge as therapeutic targets.
- Elucidation of the biological function of PMTs would be facilitated by the development of selective chemical probes; this is a compelling area for future chemical biology studies, given the paucity of available tool compounds, many of which remain to be validated in cells. In particular, the emergence of these enzyme families as therapeutic targets suggests that such chemical probes could yield lead compounds for drug development.
- Understanding the mechanisms that govern substrate specificity, especially for nonhistone targets, merits additional study.

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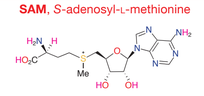
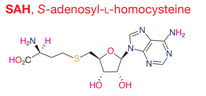
Substrates and products

SAM, *S*-adenosyl-L-methionine



SAH, *S*-adenosyl-L-homocysteine



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Poster content

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