Azathioprine ADME

Huddart, R., Jassal, B.
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 81

This document contains 1 pathway and 18 reactions (see Table of Contents)
Thiopurines were originally developed for cancer treatment in the early 1950s, with 6-mercaptopurine (6MP) being the first thiopurine approved by the FDA for the treatment of leukaemia, just two years after its discovery. Azathioprine (AZA), a prodrug of 6MP, was developed by the addition of a nitroimidazol group a few years later to bypass the high first-pass metabolism of 6MP due to oxidation in intestinal cells by xanthine oxidase (XDH). AZA is a thiopurine prodrug, and its pharmacological action is based on the release of the active metabolite 6-mercaptopurine (6MP) which is further metabolised to pharmacologically active 6-thioguanine nucleotides (6-TGNs). These 6-TGNs achieve their cytotoxic effects in one of four ways:

1. Incorporation of 6-thioguanosine triphosphate (6TGTP) into RNA
2. Incorporation of 6-thiodeoxyguanosine triphosphate (6TdGTP) into DNA
3. Inhibition of de novo purine synthesis by methylmercaptopurine nucleotides such as methylthioinosine monophosphate (meTIMP)
4. Inhibition of RAC1 by 6TGTP which induces apoptosis in activated T-cells.

While AZA has been supplanted as an antitumour drug, it remains useful as an immunosuppressant antimetabolite drug indicated to treat rheumatoid arthritis, Crohn's disease, ulcerative colitis, cancer and to prevent rejection in kidney transplant patients (Axelrad et al. 2016, Tominaga et al. 2021).

The molecular steps of AZA metabolism are described in this pathway (Cuffari et al. 1996, Dubinsky 2004). Briefly, oral AZA is rapidly converted to 6MP. Initial 6MP metabolism occurs along competing catabolic (XDH, TPMT) and anabolic (HPRT) enzymatic pathways. Once formed, 6-thiosine 5'-monophosphate (6TIMP) is further metabolized by inosine monophosphate dehydrogenase (IMPDH) and guanosine monophosphate synthetase (GMPS) to 6-thioguanosine 5’monophosphate (6TGMP). 6TGMP is then converted to the pharmacologically-active di- and tri- derivatives by their respective kinases.

**Literature references**


**Editions**

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GSH cleaves AZA to 6MP

**Location:** Azathioprine ADME

**Stable identifier:** R-HSA-9751051

**Type:** uncertain

**Compartments:** extracellular region

The GST-catalysed cleavage of azathioprine (AZA) to 6-mercaptopurine (6MP) and a nitroimidazol compound (Chalmers 1974) is prevalent at physiological pH (Von Bahr et al. 1980). Spontaneous cleavage is also possible, providing a minor contribution to AZA catabolism. Several groups have shown that biogenic thiols such as glutathione or cysteine can facilitate the first step of AZA activation, due to the presence of carboxyl, thiol, and amine groups in their molecules (Hoffmann et al. 2001, Chrzanowska et al. 2003).

**Followed by:** SLC28A2,3 cotransport 6MP and Na+ from extracellular region to cytosol, SLC29A1,2 transport 6MP from extracellular region to cytosol

**Literature references**


SLC28A2,3 cotransport 6MP and Na+ from extracellular region to cytosol

**Location:** Azathioprine ADME

**Stable identifier:** R-HSA-9751037

**Type:** transition

**Compartments:** plasma membrane, extracellular region, cytosol

Candidates for the transport of thiopurines like 6-mercaptopurine (6MP) into the cell include the sodium-dependent transporters SLC28A2 (concentrative Na(+)-nucleoside cotransporter 2, CNT2) and SLC28A3 (concentrative Na(+)-nucleoside cotransporter 3, CNT3). Down-regulation of these influx transporters may play a major role in 6MP resistance of cells (Fotoohi et al. 2006, Peng et al. 2008, Karim et al. 2011).

**Preceded by:** GSH cleaves AZA to 6MP

**Followed by:** TPMT transfers methyl group to 6MP, forming 6MeMP

**Literature references**


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SLC29A1,2 transport 6MP from extracellular region to cytosol

**Location:** Azathioprine ADME

**Stable identifier:** R-HSA-9751024

**Type:** transition

**Compartments:** plasma membrane, extracellular region, cytosol

Candidates for the transport of thiopurines like 6-mercaptopurine (6MP) into the cell include the transporters SLC29A1 (equilibrative nucleoside transporter 1, ENT1) and SLC29A2 (equilibrative nucleoside transporter 2, ENT2). Down-regulation of these influx transporters may play a major role in 6MP resistance of cells (Fotoohi et al. 2006, Peng et al. 2008, Karim et al. 2011).

**Preceded by:** GSH cleaves AZA to 6MP

**Followed by:** TPMT transfers methyl group to 6MP, forming 6MeMP

**Literature references**


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Azathioprine (AZA) was developed as a prodrug to 6-mercaptopurine (6MP) in order to counter the high first-pass metabolism of 6MP in the intestine. A nitroimidazol group was added to 6MP to create AZA. Human glutathione transferases (GSTs) A1-1, A2-2, and M1-1, all highly expressed in human liver, display high enzymatic activity towards AZA, cleaving it to release the antimetabolite 6-mercaptopurine (6MP) (Eklund et al. 2006, Moden & Mannervik 2014). After oral administration AZA is undetectable in blood, while 6MP appears after either oral or iv AZA administration (Lin et al. 1980). This is because, after ingestion, around 88% of AZA is converted to 6MP. The uncatalyzed reaction of AZA with glutathione is estimated to be <1% of the GST-catalyzed reaction. 6MP is released via a tetrahedral intermediate formed by nucleophilic attack of the glutathione thiolate (GS−). The reaction is thought to be promoted by H-bonding or other polar interactions (Zhang et al. 2012). GSTs variants may be associated with AZA efficacy and pharmacokinetics (Lufaco et al. 2019).

Followed by: XDH oxidises 6MP to 6TU, TPMT transfers methyl group to 6MP, forming 6MeMP, HPRT1 tetramer transfers phosphoribosyl group to 6MP to form 6TIMP

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6-mercaptopurine (6MP) can be metabolized via three competing pathways; oxidation by xanthine oxidase (XDH), methylation by thiopurine methyl S-transferase (TPMT) and conversion by hypoxanthine-guanine phosphoribosyltransferase (HPRT1).

6MP can be methylated to 6-methylmercaptopurine (6MeMP) by thiopurine methyltransferase (TPMT) (Weinshilboum et al. 1978). Although 6MeMP is an inactive metabolite, it is still capable of inhibiting purine biosynthesis (Hill & Bennett Jr 1980, Dervieux et al. 2001).

Genetic variability in TPMT enzyme activity is responsible for the majority of the individual differences observed in both the efficacy and toxicity of thiopurines. The TPMT gene exhibits more than 30 genetic polymorphisms that affect its enzymatic activity (Wang & Weinshilboum 2006, Colleoni et al. 2013). TPMT methylation competes with the activation pathway and influences the relative proportion of intracellular active 6-thioguanine nucleotides (6-TGNs) produced by a given individual. Patients with intermediate or absent TPMT activity can produce significantly higher concentrations of 6-TGNs, and can experience potentially life-threatening myelosuppression when treated with standard or even low dose therapy (Lennard & Lilleyman 1989, Lennard et al. 1989, Relling et al. 2011, Dean 2012).

Preceded by: SLC28A2,3 cotransport 6MP and Na+ from extracellular region to cytosol, SLC29A1,2 transport 6MP from extracellular region to cytosol, GST dimers cleave AZA to 6MP

Literature references

6-mercaptopurine (6MP) can be metabolized via three competing pathways; oxidation by xanthine oxidase (XDH), methylation by thiopurine methyl S-transferase (TPMT) and conversion by hypoxanthine-guanine phosphoribosyltransferase (HPRT1).

6-mercaptopurine (6MP) is subjected to high first-pass metabolism due to oxidation in intestinal cells and liver cells by xanthine oxidase (XDH) (Saksela & Raivio 1996, Yamaguchi et al. 2007, Choughule et al. 2014). This reaction produces an inactive metabolite 6-thiouric acid (6TU, via 8-OH-6MP), which is excreted in urine. Patients with low XDH expression can exhibit elevated levels of the toxic antimetabolite 6MP which might result in a higher risk of thiopurine-induced adverse effects (Ding et al. 2021).

**Preceded by:** GST dimers cleave AZA to 6MP

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6-mercaptopurine (6MP) can be metabolized via three competing pathways; oxidation by xanthine oxidase (XDH), methylation by thiopurine methyl S-transferase (TPMT) and conversion by hypoxanthine-guanine phosphoribosyltransferase (HPRT1).

Hypoxanthine-guanine phosphoribosyltransferase tetramer (HPRT1) catalyzes the transfer of phosphoribosyl from 5-phosphoribosyl 1-pyrophosphate (PRPP) to 6-mercaptopurine (6MP), to form 6-thioinosine 5’-monophosphate (6TIMP) (Krenitsky et al. 1969, Xu et al. 1997). This is the metabolic branch for the formation of the pharmacologically active 6-thioguanine nucleotides (6-TGNs).

**Preceded by:** GST dimers cleave AZA to 6MP

**Followed by:** ABCC5 transports TPMP substrates from cytosol to extracellular region, TPMT transfers methyl group to 6TIMP, forming 6MeTIMP, ABCC4 transports TPMP substrates from cytosol to extracellular region, IMPDH tetramers dehydrogenate 6TIMP to 6TXMP

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Thiopurine methyltransferase (TPMT) can methylate thiopurine drugs and its metabolites (Weinshilboum et al. 1978). The methylation of 6-thioinosine 5'-monophosphate (6TIMP) leads to formation of 6-methylthioinosine monophosphate (6MeTIMP). Although an inactive metabolite in terms of inhibiting DNA and RNA synthesis, 6MeTIMP is still capable of inhibiting purine de novo synthesis (Bökkerink et al. 1993, Karim et al. 2013).

**Preceded by:** HPRT1 tetramer transfers phosphoribosyl group to 6MP to form 6TIMP

**Followed by:** ABCC5 transports TPMP substrates from cytosol to extracellular region, ABCC4 transports TPMP substrates from cytosol to extracellular region

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IMPDH tetramers dehydrogenate 6TIMP to 6TXMP

**Location:** Azathioprine ADME

**Stable identifier:** R-HSA-9748945

**Type:** transition

**Compartments:** cytosol

Inosine 5′-monophosphate dehydrogenase (IMPDH) is a key enzyme in the de novo synthesis of guanine nucleotides and is positioned at the branch point between adenine and guanine biosynthesis. It is also strategically positioned in the metabolic pathway of thiopurines. IMPDH is considered to be the rate-limiting enzyme in the metabolism of thiopurine drugs to 6-thioguanine nucleotides (6-TGNs) (Leyva et al. 1976). IMPDH dehydrogenates 6-thioinosine 5′-monophosphate (6TIMP) to 6-thioxanthosine 5′-monophosphate (6TXMP), an intermediate metabolite in the formation of 6-TGNs.

**Preceded by:** HPRT1 tetramer transfers phosphoribosyl group to 6MP to form 6TIMP

**Followed by:** ABCC5 transports TPMP substrates from cytosol to extracellular region, GMPS dimer transforms 6TXMP to 6TGMP

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https://reactome.org
ABCC4 transports TPMP substrates from cytosol to extracellular region

**Location:** Azathioprine ADME

**Stable identifier:** R-HSA-9750546

**Type:** transition

**Compartments:** plasma membrane, extracellular region, cytosol

ABCC4 is a multidrug resistance protein (MRP4) which can transport a wide range of organic anions but especially nucleotides and nucleotide analogues. When overexpressed, ABCC4 can lower the intracellular concentration of nucleoside/nucleotide analogues such as 6-mercaptopurine (6MP), after its conversion into its respective nucleotides (Wielinga et al. 2002, Ritter et al. 2005, Peng et al. 2008). This may lead to an impaired ability of 6MP to inhibit cell proliferation.

**Preceded by:** GMPS dimer transforms 6TXMP to 6TGMP, TPMT transfers methyl group to 6TIMP, forming 6MeTIMP, HPRT1 tetramer transfers phosphoribosyl group to 6MP to form 6TIMP

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ABCC5 transports TPMP substrates from cytosol to extracellular region

Location: Azathioprine ADME

Stable identifier: R-HSA-9750617

Type: transition

Compartments: plasma membrane, extracellular region, cytosol

ABCC5 is a multidrug resistance protein (MRP5) which can transport a wide range of organic anions but especially nucleotides and nucleotide analogues. When overexpressed, ABCC5 can lower the intracellular concentration of nucleoside/nucleotide analogues such as 6-mercaptopurine (6MP), after its conversion into its respective nucleotides (Wijnholds et al. 2000, Ritter et al. 2005, Peng et al. 2008). This may lead to an impaired ability of 6MP to inhibit cell proliferation.

Preceded by: GMPS dimer transforms 6TXMP to 6TGMP, TPMT transfers methyl group to 6TIMP, forming 6MeTIMP, IMPDH tetramers dehydrogenate 6TIMP to 6TXMP, HPRT1 tetramer transfers phosphoribosyl group to 6MP to form 6TIMP

Literature references


Editions

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GMPS dimer transforms 6TXMP to 6TGMP

Location: Azathioprine ADME

Stable identifier: R-HSA-9748957

Type: transition

Compartments: cytosol

GMP synthase (glutamine-hydrolyzing) (GMPS) is involved in the de novo synthesis of guanine nucleotides which are not only essential for DNA and RNA synthesis, but also provide GTP for cellular processes. GMPS forms a dimer and can act on many drugs that are nucleobase- and nucleoside-based compounds (Welin et al. 2013). Here, 6-thioxanthosine 5'-monophosphate (6TXMP) is transformed to 6-thioguanosine monophosphate (6TGMP), the first 6-thioguanine nucleotide (6-TGN).

Preceded by: IMPDH tetramers dehydrogenate 6TIMP to 6TXMP

Followed by: ABCC5 transports TPMP substrates from cytosol to extracellular region, ABCC4 transports TPMP substrates from cytosol to extracellular region, GUK1 phosphorylates 6TGMP to 6TGDP

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**GUK1 phosphorylates 6TGMP to 6TGDP**

**Location:** Azathioprine ADME

**Stable identifier:** R-HSA-9748949

**Type:** transition

**Compartments:** cytosol

6-thioguanine nucleotides (6-TGNs) consist of 6-thio(deoxy)guanosine 5'-monophosphate (T(d)GMP), -diphosphate (T(d)GDP), and -triphosphate (T(d)GTP), representing the pharmacologically-active metabolites involved in drug action of thiopurines.

Guanylate kinase (GUK1) is an essential nucleoside monophosphate kinase that catalyzes the phosphorylation of guanine-monophosphate (GMP) to yield GDP, an important precursor for nucleotide synthesis (Agarwal et al. 1978). As well as this physiological role, GUK1 converts therapeutic prodrugs into their pharmacologically active metabolites. In this example, GUK1 phosphorylates 6-thioguanosine monophosphate (6TGMP) to 6-thioguanosine diphosphate (6TGDP) (Miller et al. 1977, review in Karran 2006).

**Preceded by:** GMPS dimer transforms 6TXMP to 6TGMP

**Followed by:** NME1:2 hexamer phosphorylates 6TGDP to 6TGTP

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NME1:2 hexamer phosphorylates 6TGDP to 6TGTP

Location: Azathioprine ADME

Stable identifier: R-HSA-9748999

Type: transition

Compartments: cytosol

6-thioguanine nucleotides (6-TGNs) consist of 6-thio(deoxy)guanosine 5'-monophosphate (T(d)GMP), -diphosphate (T(d)GDP), and -triphosphate (T(d)GTP), representing the pharmacologically-active metabolites involved in drug action of thiopurines.

Nucleoside diphosphate kinase (NME) plays a major role in the synthesis of nucleoside triphosphates other than ATP. NME1 forms a hexameric complex with NME2 and this complex is thought to phosphorylate 6-thioguanosine diphosphate (6TGDP) to 6-thioguanosine triphosphate (6TGTP) (Karner et al. 2010).

Preceded by: GUK1 phosphorylates 6TGMP to 6TGDP

Followed by: p-VAV1,2,3 exchange 6TGTP for GDP on RAC1

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Guanylate kinase (GUK1) is an essential nucleoside monophosphate kinase that catalyzes the phosphorylation of deoxyguanosine-monophosphate (dGMP) to yield dGDP, an important precursor for nucleotide synthesis (Agarwal et al. 1978). As well as this physiological role, GUK1 converts therapeutic produgs into their pharmacologically active metabolites. In this example, GUK1 phosphorylates 6-thiodeoxyguanosine monophosphate (6TdGMP) to 6-thiodeoxyguanosine diphosphate (6TdGDP) (Miller et al. 1977, review in Karran 2006).

Preceded by: NUDT15 dimer dephosphorylates 6TdGTP to 6TdGMP

Followed by: NME1:2 hexamer phosphorylates 6TdGDP to 6TdGTP

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Nucleoside diphosphate kinase (NME) plays a major role in the synthesis of nucleoside triphosphates other than ATP. NME1 forms a hexameric complex with NME2 and this complex is thought to phosphorylate 6-thiodeoxyguanosine diphosphate (6TdGDP) to 6-thiodeoxyguanosine triphosphate (6TdGTP) (Karner et al. 2010).

**Preceded by:** GUK1 phosphorylates 6TdGMP to 6TdGDP

**Followed by:** NUDT15 dimer dephosphorylates 6TdGTP to 6TdGMP

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NUDT15 dimer dephosphorylates 6TdTGTP to 6TdTGMP

Location: Azathioprine ADME

Stable identifier: R-HSA-9750555

Type: transition

Compartments: cytosol

Nucleotide triphosphate diphosphatase (NUDT15) is thought to catalyze the hydrolysis of nucleoside triphosphates, including the prodrug thiopurine derivatives 6-thio-dGTP and 6-thio-GTP, and stops their incorporation into DNA and RNA respectively (Kasumi et al. 1993, Carter et al. 2015, Hashiguchi et al. 2018). Polymorphisms in NUDT15 are associated with thiopurine intolerance in Asian populations (Tanaka & Saito 2021). Defective NUDT15 alleles show excessive levels of thiopurine active metabolites and toxicity (Moriyama et al. 2016).

Preceded by: NME1:2 hexamer phosphorylates 6TdTGDP to 6TdTGTP

Followed by: GUK1 phosphorylates 6TdTGMP to 6TdTGDP

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p-VAV1,2,3 exchange 6TGTP for GDP on RAC1

**Location:** Azathioprine ADME

**Stable identifier:** R-HSA-9751201

**Type:** transition

**Compartments:** plasma membrane, cytosol

The guanine nucleotide exchange factors 1-3 (VAV1,2,3) act as guanine nucleotide exchange factors (GEFs) for Ras-related C3 botulinum toxin substrate (RAC1), catalysing the exchange of bound GDP for GTP (Heo et al. 2005, Jaiswal et al. 2013). To be fully active, VAV proteins are tyrosine-phosphorylated (Teramoto et al. 1997).

One of the active metabolites of azathioprine (6-thioguanosine triphosphate, 6TGTP) can block RAC1 activity by binding to it instead of GTP (presumably mediated by VAV proteins), thus converting a costimulatory signal into an apoptotic signal (Tiede et al. 2003).

**Preceded by:** NME1:2 hexamer phosphorylates 6TGDP to 6TGTP

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</tbody>
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https://reactome.org
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Introduction 1

Azathioprine ADME

- GSH cleaves AZA to 6MP 2
- SLC28A2,3 cotransport 6MP and Na+ from extracellular region to cytosol 4
- SLC29A1,2 transport 6MP from extracellular region to cytosol 5
- GST dimers cleave AZA to 6MP 6
- TPMT transfers methyl group to 6MP, forming 6MeMP 7
- XDH oxidises 6MP to 6TU 8
- HPRT1 tetramer transfers phosphoribosyl group to 6MP to form 6TIMP 9
- TPMT transfers methyl group to 6TIMP, forming 6MeTIMP 10
- IMPDH tetramers dehydrogenate 6TIMP to 6TXMP 11
- ABCC4 transports TPMP substrates from cytosol to extracellular region 12
- ABCC5 transports TPMP substrates from cytosol to extracellular region 13
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- GUK1 phosphorylates 6TGMP to 6TGDP 15
- NME1:2 hexamer phosphorylates 6TGDP to 6TGTP 16
- GUK1 phosphorylates 6TdGMP to 6TdGDP 17
- NME1:2 hexamer phosphorylates 6TdGDP to 6TdGTP 18
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