Azathioprine ADME

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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.

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Literature references


Reactome database release: 79

This document contains 1 pathway and 18 reactions (see Table of Contents)
Azathioprine ADME

Stable identifier: R-HSA-9748787

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


GSH cleaves AZA to 6MP

Location: Azathioprine ADME

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