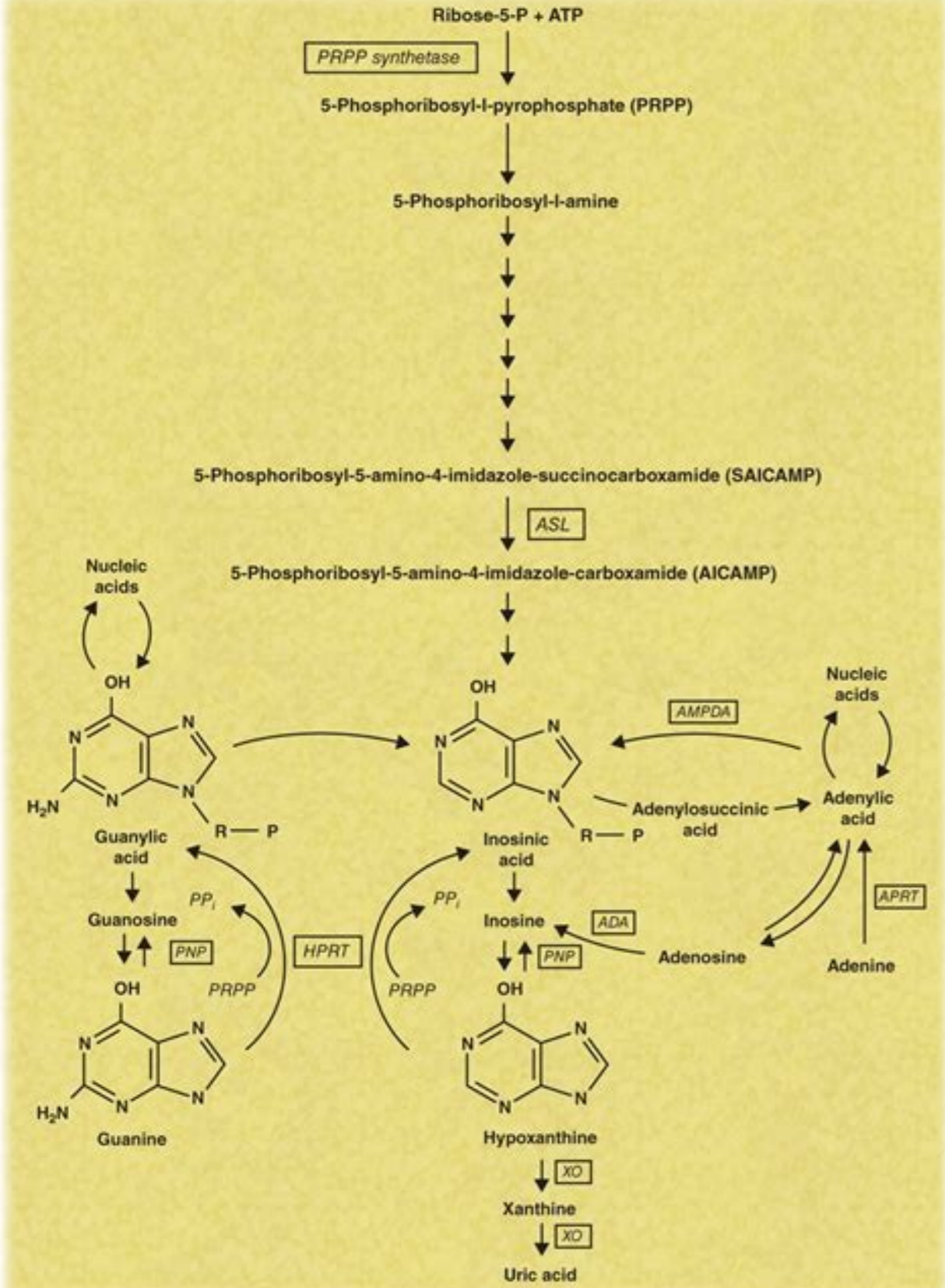


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Review
Yeast to Study Human Purine Metabolism Diseases

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Abstract: Purine nucleotides are involved in a multitude of cellular processes, and the dysfunction of purine metabolism has drastic physiological and pathological consequences. Accordingly, several genetic disorders associated with defective purine metabolism have been reported. The etiology of these diseases is poorly understood and simple model organisms, such as yeast, have proved valuable to provide a more comprehensive view of the metabolic consequences caused by the identified mutations. In this review, we present results obtained with the yeast *Saccharomyces cerevisiae* to exemplify how a eukaryotic unicellular organism can offer highly relevant information for identifying the molecular basis of complex human diseases. Overall, purine metabolism illustrates a remarkable conservation of genes, functions and phenotypes between humans and yeast.

Keywords: purine metabolism; nucleotide synthesis; purine-associated deficiencies; hyperuricemia; Lesch–Nyhan; AMP-deaminase; ATIC; ADSL; PRPS

1. Introduction

Purine nucleotides, adenosine 5'-triphosphate (ATP), guanosine 5'-triphosphate (GTP) and their derivatives are involved in a myriad of cellular processes: energy storage, synthesis of nucleic acids and coenzymes (Nicotinamide adenine dinucleotide (NAD)/Nicotinamide adenine dinucleotide phosphate (NADP)/coenzyme A/flavin adenine dinucleotide (FAD)), translation, signaling, etc. These molecules are thus absolutely required for all known forms of life, and their synthesis results essentially from conserved pathways. In yeast, mutations abolishing ATP or GTP synthesis are lethal, although lethality may require more than one mutation due to genetic and pathway redundancy [1]. Even a partial block of purine metabolism can have drastic physiological consequences, and several diseases associated with purine metabolism dysfunctions have been reported in human [2–5]. Some purine metabolic disorders have been described for a long time, such as hyperuricemia (gout), which is caused by an excess of uric acid (the final purine degradation product) leading to a painful deposit of urate crystals in joints. Among the studies of genetic alterations leading to hyperuricemia, hypoxanthine phosphoribosyl transferase (HGPRT)-deficiency, involved in the Lesch–Nyhan syndrome, was one of the very first genetic-disease enzymes identified in humans [6]. In addition to hyperuricemia, purine metabolism-associated diseases share a large spectrum of immunological, hematological and neuro-muscular disorders [7], and are all characterized by an abnormal level of purine nucleotides in cells and of nucleosides and/or nucleobases in bodily fluids [8]. In most cases, the dysfunctional gene in purine metabolism is known. However, this identification of the causative enzyme does not necessarily give clear indications on the etiology of the disease and hence, a more comprehensive view of the metabolic consequences of the dysfunction is often needed. To this end, model organisms that are amenable to genetics

Canine Cyclic Hematopoiesis is Associated with Abnormal Purine and Pyrimidine Metabolism

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ABSTRACT: Canine cyclic hematopoiesis is an autosomal recessive disease characterized by regular 11–13-d cycles of the neutrophil, reticulocyte, and platelet counts caused by a defect in regulation of marrow stem cell proliferation. Treatment with lithium abrogates cycling of the cell counts in these grey collie dogs. Aware of the defective lymphoploids associated with adenosine deaminase and purine nucleoside phosphorylase deficiencies, we hypothesized that abnormal purine or pyrimidine metabolism might be present in these dogs. Using high pressure liquid chromatography, we measured erythrocyte purine and pyrimidine nucleotide levels and plasma purine and pyrimidine nucleosides and bases in normal and grey collie dogs before and during lithium treatment.

During neutropenic periods in the grey collie, erythrocyte ATP, GTP, and UTP levels were significantly elevated. Normal dogs made neutropenic with cyclophosphamide did not show such elevations. Lithium treatment normalized the levels of erythrocyte ATP, GTP, and UTP in the grey collies and eliminated the differences between normal and grey collie nucleotide levels. Plasma thymine levels were markedly increased during neutropenia in the grey collie but were not increased in cyclophosphamide-treated normal dogs. The finding of abnormal concentrations of purine and pyrimidine metabolites in these dogs suggest that a metabolic derangement in purine or pyrimidine metabolism may be the cause of the defective stem cell proliferation in this disease.

INTRODUCTION

Cyclic hematopoiesis in grey collie dogs is an autosomal recessive disorder in which regular 11–13-d cycles of the neutrophil count lead to severe infections

and early death. The cyclic fluctuation of the neutrophil count is reproducible and is reliably associated with fluctuations in eosinophils, monocytes, lymphocytes, platelets, and reticulocytes (1–4). These periodic changes are caused by alterations in marrow cell production rates rather than alterations in rates of destruction or sequestration of cells in the circulation (5, 6–8). Studies of granulocytic and erythroid precursor cells have shown fluctuations in these committed progenitor cell populations over the cycle of cell counts but have not explained the mechanism(s) causing cyclic hematopoiesis (7–11). Bone marrow transplantation experiments have shown that this disease can be cured or transferred to a normal littermate by irradiation and marrow cell infusion, clearly implicating the marrow stem cell pool(s) as the site of the defect (12–14). Recently we have demonstrated that lithium carbonate eliminates the severe recurrent neutropenia, smooths the fluctuations of other cell counts, and eliminates the marked cycling of neutrophil colony-forming cells in these dogs (15, 16).

In autosomal recessive disorders where the biochemical defect has been identified, it usually involves an enzyme protein. Drawing an analogy with the defective lymphoploids associated with adenosine deaminase (ADA) (17) and purine nucleoside phosphorylase (PNP) (18) deficiency, we reasoned that a similar phenomenon of abnormal purine metabolism might be present in cyclic hematopoiesis. Studies of patients with inherited immune deficiency have shown that the absence of ADA is associated with combined T and B lymphocyte dysfunction and the absence of PNP is associated with a severe T cell defect and normal B cell function (19). It is generally accepted that the accumulation of dATP in ADA deficiency and deoxy-

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*Abbreviations used in this paper: ADA, adenosine deaminase; CC, grey collie; HGPRT, hypoxanthine guanine phosphoribosyl transferase; ND, normal dog; NP, purine nucleoside phosphorylase; PMN, neutrophils.

