Klin. Biochem. Metab., 13 (34), 2005, No. 4, p. 177–181.

Purine *de novo* Synthesis – Mechanisms and Clinical Implications

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SUMMARY
Purine *de novo* synthesis represents a basis for nucleotide metabolism as well as all other interconnected pathways. Synthesis of the purine ring *de novo* is required especially when DNA is replicated so that, although present in most tissues, the activity of the metabolic pathway is highly variable. Since the key experiments to discover functioning of the pathway were conducted in the fifties, it attracts substantial attention of researchers because inhibitors of the pathway are effective drugs against cancer, inflammatory disorders and various infections. There is substantial body of information on genes, proteins involved and regulation, however some questions concerning substrate channeling and interaction of the proteins remain open.
Key words: purine, de novo, biosynthesis, metabolism, cancer, inhibitor.

1. Introduction

Purine *de novo* synthesis (PDNS) represents a basis for all other steps in nucleotide metabolism as well as all other interconnected pathways. Despite the essential functions of PDNS, salvage pathways recycle nucleotides to meet daily needs. Thus, the requirement to synthesize new purines in differentiated cells is small. Purine *de novo* synthesis of the purine ring is required only when DNA is replicated so that, although present in most tissues, the activity of the metabolic pathway is highly variable.

The purine biosynthetic pathway is nearly ubiquitous among organisms and results in the conversion of phosphoribosyl pyrophosphate (PRPP) to inosine monophosphate (IMP). The key experiments to discover functioning of the pathway had been conducted by John Buchanan and his co-workers in the 1950s (1–3). They established in pigeon liver extracts that 10 enzymatic activities are required for the interconversion of PRPP to IMP (Fig. 1). In contrast, in most microorganisms, 12 enzymatic activities are involved in the same interconversion.

In uricotelic species (e. g. in the liver of birds and terrestrial reptiles), purines synthesized *de novo* are oxidized to uric acid and excreted as the main form of waste nitrogen. In plants, specialized tissues use it to assimilate and detoxify NH_3.

It is assumed that the content of ATP and GTP in mammalian cells equals to about 15–20% of the number of purine bases incorporated into DNA during replication. Hence, it is difficult for the cell to replicate the genome in the presence of a complete block of *de no-*

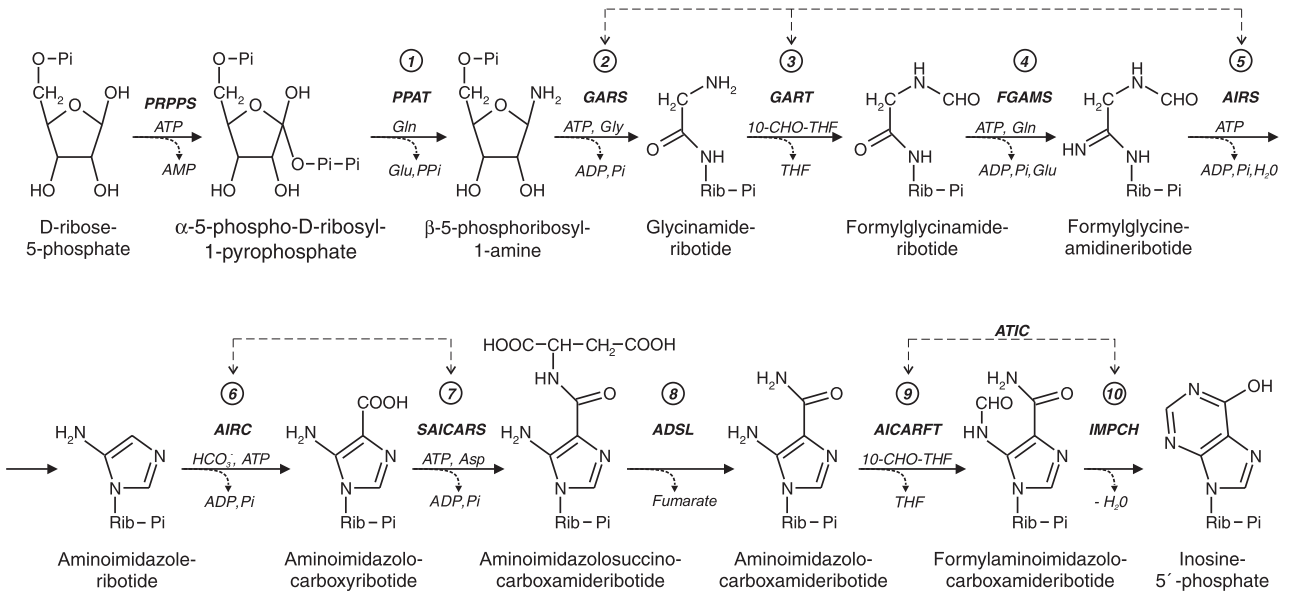

Fig. 1. Scheme of purine *de novo* synthesis. For abbreviation of enzyme names see text (section 3. Proteins). Multifunctional enzymes shown in dashed lines. THF – tetrahydrofolate, 10-CHO-THF - 10-formyl-tetrahydrofolate.

vo purine synthesis. It is not surprising that PDNS attracted substantial attention in the anticancer drug research.

The aim of this article is to briefly review the most important literature dealing with genes, proteins, intermediates, regulative mechanisms and clinical implication of purine *de novo* synthesis and update our knowledge of this important metabolic pathway.

2. Genes

A cluster of genes (acting as an operon) encoding enzymes of PDNS in an approximately 16-kilobase pair region of the *Bacillus subtilis* chromosome was cloned (4). Sequence comparisons provided evidence for homology with the corresponding multifunctional enzymes from yeast and *Drosophila*. Sequence alignment of the phosphoribosylaminoimidazole carboxylase heterodimer from *Bacillus subtilis* with the monomeric enzyme from *Methanobrevibacter smithii* indicated an evolutionary relationship between the two enzymes.

The human genes or cDNAs for all the enzymes involved in the *de novo* pathway have been isolated by Patterson and co-workers (5). Six genes encode the enzymes. Three of these genes in vertebrates code for multifunctional enzymes (see Fig. 1). Except the enzyme for step one (regulatory), which has been found to be closely linked to bifunctional enzyme (steps six and seven) on human chromosome 4, all genes for the pathway are on different chromosomes.

The bovine cDNA sequences of seven known genes involved in the PDNS are highly similar to the human genes and their chromosomal locations are in accordance with comparative positions of the human genes. This supports the hypothesis that genes involved in basic biological functions are conserved.

Isolation of clones showed the multifunctional nature of some enzymes in the pathway (6) and revealed possible coordinate regulation of these genes (e. g. 7).

The processed pseudogene sequences of genes of PDNS identified in several mammalian species indicate that the genes of this pathway have been susceptible to retrotransposition.

3. Proteins

In mammals, the first ten steps are catalyzed by six different enzymes; three monofunctional, two bifunctional and one trifunctional enzyme (see Fig. 1). Phosphoribosyl pyrophosphate amidotransferase (PPAT, EC 2.4.2.14) catalyses step 1 and it is a regulative step (see below). Trifunctional enzyme glycinamide ribonucleotide synthetase-glycinamide ribonucleotide transformylase-aminoimidazole ribonucleotide synthetase (GARS-GART-AIRS, EC 6.3.4.13, 2.1.2.2, 6.3.3.1) catalyzes steps 2, 3 and 5; formylglycinamidine ribonucleotide synthase (FGAMS, EC 6.3.5.3) step 4. Aminoimidazole ribonucleotide carboxylase-aminoribosyl aminoimidazole succinocarboxamide ribonucleotide synthetase (AIRC-SAICARS, EC 4.1.1.21, 6.3.2.6) catalyzes steps 6 and 7 and adenylosuccinate lyase (ADSL, EC 4.3.2.2) catalyzes step 8. The ADSL also catalyzes the second of the two steps converting IMP to AMP. Bifunctional aminoimidazolecarboxamide ribonucleotide formyltransferase – IMP cyclohydrolase (AICARFT-IMPCH or ATIC, EC 4.1.1.21, 6.3.2.6) catalyzes steps 9 and 10. ATIC requires dimerisation for AICARFT activity but not for IMPCH activity. Formyl--AICAR was found to be a product inhibitor of AICARFT with submicromolar K(i). The transformylase reaction strongly favors the substrate. The coupling of the AICARFT and IMPCH activities on a single polypeptide allows the overall conversion of AICAR to IMP to be favorable by coupling the unfavorable formation of FAICAR with the highly favorable cyclization reaction (8).

PDNS is not expressed in all cell types in man. It is highly active in muscle and liver. On the other hand, human erythrocyte and matured brain are not capable of PDNS and rely solely on salvage.

4. Intermediates

Behind the first committed step of PDNS, the intermediates of the pathway do not participate in other metabolic reactions aside the pathway. Two intermediates are chemically unstable – phosphorybosylamine (PRA, $t_{1/2}$ is 5s under physiological conditions) and formylglycinamidine ribonucleotide and others are putatively unstable (carboxyminoimidazole ribonucleotide and aminoimidazole ribonucleotide). It has substantial implications for discussions about substrate channeling in the pathway (see bellow). Succinylaminoimidazolecarboxamide ribotide (SAICAR) in the dephosphorylated form has been suggested to cause neurological impairment in patients with inherited defects associated with its accumulation (ADSL deficiency or fumarase deficiency).

Aminoimidazolecarboxamide ribotide (AICAR also termed ZMP), the intermediate of the pathway and the dephosphorylated ribonucleoside (AICA riboside also termed acadesine as a drug), are of particular interest because of its similarity to AMP and adenosine, respectively. AICA riboside are easily transported across the cellular membrane via equilibrate nucleoside transporter, it is intracellularly phosphorylated and can reach intracellularly the millimolar levels.

Vast number of effects of AICA riboside and AICAR on cellular functions have been reported. Competition between AICA riboside and adenosine for this transporter results in the accumulation of extracellular adenosine that inhibits excitatory synaptic transmission via activation of inhibitory adenosine A1 receptors. AICAR activates the AMP-activated protein kinase, AMPK kinase and glycogen phosphorylase (9). Effects of AICA riboside include accelerated repletion of purine nucleotide pools in the heart, inhibition of growth and depletion of pyrimidine nucleotide pools in fibroblasts, reduction of endurance in skeletal muscle, inhibition of fatty acid, sterol synthesis, and gluconeogenesis in hepatocytes, and increase in glucose uptake in muscle. Acadesine can either induce or inhibit apoptosis depending on the cell type (10). This compound has important implications in the context of treatment of leukemia (11), diabetes, cardioprotection (12) and as an immunomodulator (13).

5. Inhibitors

Potent inhibitors of purine (as well as pyrimidine) nucleotide biosynthesis are synthetic or natural-product analogues of intermediates of the pathway or, more recently, inhibitors rationally designed from the knowledge of the catalytic mechanism. These inhibitors are effective drugs against cancer, inflammatory disorders and various infections. For human cancer, the purine pathway is a more traditional target for inhibition than the pyrimidine pathway, where more toxic side effects are apparent. Drugs such as methotrexate (inhibiting transformylation steps 3 and 9) have multiple sites of action, making it difficult to predict quantitatively their effects upon cells. Rational design of inhibitors based on the X-ray structure of the target enzyme has the chance of yielding drugs with only one site of action in human cells. That approach resulted in the discovery of drugs acting against PPAT (step 1; e. g. piritrexm), GART (azaserine, diazomycin, dideazatetrahydrofolate, lometrexol), AIRC (fluorosulfonylbenzoyl-adenosine) and SAICARS (nitroaminoimidazole ribonucleotide).

PDNS inhibitors had been proved to cause the disappearance of intracellular nucleotides and accumulation of PDNS intermediates to a milimolar concentration level.

6. Control

The knowledge of control mechanisms of pathways is important for understanding of biochemical processes and it has also substantial implications for the treatment of diseases. The biosynthesis pathways are generally negatively regulated by their end products. The regulation in general occurs at two distinct levels – feedback inhibition of usually the first enzyme of the pathway and coordinate repression at the transcriptional level of the genes encoding enzymes of the pathway. Transcription of the *Bacillus subtilis* purine *de novo* operon has been known to be regulated by adenine and guanine nucleotides (4). The PDNS pathway is co-regulated with genes involved in biosynthesis of substrates (glutamine, glycine and 10-formyl tetrahydrofolate) consumed in the pathway (14).

In *Saccharomyces cerevisiae*, PDNS genes are transcriptionally activated by Bas1p and Bas2p transcription factors; intermediate SAICAR is needed for optimal activation of the genes (15).

Human PDNS in lymphoblasts had been studied by Hershfield and Seegmiller (16). They found coordinate control of proximal (rate-determining) steps and the inosinic acid branch point. Becker and Kim lately reported the control by purine nucleotides and phosphoribosylpyrophosphate in human fibroblasts (17). Retroinhibition of human amidophosphoribosyltransferase by purine nucleotides was shown to play an important role in cellular proliferation (18). Expression of all the enzymes was found to be upregulated after the treatment with keratinocyte and epidermal growth factors, indicating that these mitogens stimulate nucleotide production by induction of these enzymes. It is also known that PDNS enzymes (contrary to salvage enzymes) display a variable activity during cell cycle with peak values in the log phase (19).

7. Channeling

Substrate channeling by multienzyme complexes or multifunctional enzymes is a widely accepted concept. Unstable intermediates and multifunctional enzymes involved in PDNS point toward channeling of substrates of the pathway. There is also a number of experimental data supporting the theory of substrate channeling in PDNS. Some proteins co-purify during isolation procedures in avian liver and human lymphocytes (20).

However, other experiments found no stable interaction between PPAT and GARS between which unstable PRA has to channel. The authors concluded that interaction should be transient (21).

It has also been confirmed that in the last two steps (AICAR-FAICAR-IMP) the substrate does not channel and binding sites do not communicate. The authors speculate that the reason for bifunctionality of the protein is increased local concentration of the intermediate and that coupling of the activities on a single polypeptide allows the overall conversion of AICAR to IMP to be favorable (22, see also section 3. Proteins). Substrate channeling in PDNS has still been the matter of hot debate.

8. Inherited metabolic disorders

There are three inherited metabolic defects discovered so far related to the pathway – two enzyme deficiencies (ASL and ATIC) and superactivity of phosphoribosyl pyrophosphate synthase – co-regulative step of the pathway preceding PPAT. The deficiency of ASL was discovered by Jaeken and Van den Berghe twenty years ago (23). The major clinical feature is variable psychomotor delay often accompanied by epilepsy and autistic features. The second deficiency (ATIC) has been described recently by Van Den Berghe's group (24). Findings of normal uric acid level in the body fluids of patients confirm that enzyme defects (besides of first regulative step) in PDNS do not effect overall metabolic flux of the pathway as predicted by mathematical model (25). In both the disorders, substrates of defective enzymes accumulate in body fluids of the patients and are the key biochemical hallmarks.

Superactivity of phosphoribosyl pyrophosphate synthase is an X chromosome-linked disorder characterized by PRPP, purine nucleotide, and uric acid overproduction. Clinically it is manifested as gout and, in some cases, with neurodevelopmental impairment (26). The mechanisms underlying the inherited PRS superactivity are diverse and include defective allosteric regulation, increased apparent affinity of PPAT for the substrate phosphoribosyl pyrophosphate, and increased activity of one of the two isoforms of the enzyme (caused by pretranslational dysregulation of expression).

9. Conclusions

The aim of this communication was to review the most important literature dealing with mechanisms and clinical implication of purine *de novo* synthesis and update our knowledge of this important metabolic pathway. Despite an extensive research of purine *de novo* synthesis conducted over more than half a century by principal

investigators and numerous papers published in prominent journals, the functionality of the pathway has not been fully understood yet. Over fifty papers, including fourteen in journals with impact factors between 4 and 11 retrieved by PubMed for the keyword "purine biosynthesis" published over last four months stress that the interest in the pathway has not been declining.

Genes and enzymes involved in the pathway have been well characterized by now. Some properties of the pathway, e. g. feedback inhibition by products of the pathway, belong to a biochemical canon. On the other hand, the channeling of intermediates in the pathway still remains open. The rationally designed inhibitors based on the X-ray structure of the target enzyme provide drugs with only one site of action in human cells including the pathway. In the pathway there are recognized only two inherited metabolic deficiencies out of ten potential offering the field for further research.

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Acknowledgement: I am grateful to Prof. Pavel Peč (Olomouc) for helpful comments and suggestions.

This work was supported by grants IGA NR/7796-3 and MSM6198959205.

Do redakce došlo 25. 2. 2005.

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Tematický plán kurzů Katedry klinické biochemie IPVZ pro období říjen 2005 – červen 2006 (část 6)

211018 Kurz – Práce s Národním a lokálním číselníkem laboratorních položek, tvorba Laboratorní příručky v papírovém a hypertextovém tvaru

Určeno pro pracovníky laboratoří klinické biochemie, hematologie, imunologie a mikrobiologie.
Předběžný program: Práce s NČLP, tvorba LČLP, vazba NČLP na LČLP, tvorba škál, podklady pro preanalytickou fázi, tvorba vazeb mezi položkami, příprava tabulek pro Laboratorní příručku, generování tabulek Laboratorní příručky v papírové a textové formě.Tvorba sestav, generování číselníků pro datový standard a pro spolupracující LIS nebo NIS. Praktická cvičení v počítačové učebně. Určeno pokročilým i mírně pokročilým. Volně navazuje na kurz 22. 5. 2006.
Vedoucí kurzu: ing. M. Zámečník
Termín konání: 23. 5. 2006
Místo konání: Praha 4, Budějovická 15
Kurzovné: 600,– Kč

211019 Kurz – Příprava klinických laboratoří k akreditaci II.

Určeno pro pracovníky laboratoří klinické biochemie, hematologie, imunologie a mikrobiologie.
Předběžný program: Aktuální informace o procesu přípravy klinických laboratoří na akreditace podle ISO 15189 a Národních standardů pro akreditaci klinických laboratoří. Výklad normy ISO 15189 a norem souvisejících, vytváření příručky jakosti, směrnic, standardních operačních postupů, laboratorní příručky a ostatních dokumentů, tvorba dokumentů na příkladě systému SLP. Změny, které je nutné realizovat v laboratoři. Etapy přípravy a vlastní akreditace. Zkušenosti z praxe. Praktická cvičení v počítačové učebně.
Vedoucí kurzu: ing. M. Zámečník
Termín konání: 24.–25. 5. 2006
Místo konání: Praha 4, Budějovická 15
Kurzovné: 1000,– Kč

211020 Kurz – Oxidační stres, volné radikály, teorie, klinika, vyšetřovací metody

Určeno pro pracovníky laboratorního komplementu.
Předběžný program: Teorie vzniku a působení volných radikálů, oxidační stres, klinické aspekty onemocnění na bázi oxidačního stresu, kritické hodnocení a výběr metod vyšetření, indikace, interpretace.
Vedoucí kurzu: prof. MUDr. M. Engliš, DrSc.
Termín konání: 1. 6. 2006
Místo konání: Praha 4, Budějovická 15
Kurzovné: 300,– Kč

211021 Kurz – Inovační kurz pro laboranty

Určeno pro laboranty komplementu.
Předběžný program: Vyšetřovací metody, interpretace, klinika. Volné lehké řetězce v séru (analytický přístup, volba přístrojové techniky, hodnocení); cystatin C (současné možnosti využití v nefrologii); protein S 100B (metody stanovení, interpretace u onemocnění CNS se zvláštním zřetelem k poranění CNS, vyšetření v likvoru a u novorozenců; ischémií modifikovaný albumin a jiné markery prenekrotické ischémie myokardu; nové nádorové markery; současný význam a přínos vyšetřování natriuretických hormonů z aspektu diagnostiky srdeční dysfunkce a selhání, význam stanovení natriuretických hormonů jako prognostických ukazatelů. Verifikace a validace metod z aspektu reálných podmínek laboratorního provozu, návaznost, nejistota měření v praxi, účast laborantů v přípravě certifikace a akreditace pracoviště, nejčastější chyby a interference v praxi. Zaměřeno ke specifitě práce laborantů v procesu analýzy i klinické aplikace.
Vedoucí kurzu: prof. MUDr. M. Engliš, DrSc.
Termín konání: 8.–9. 6. 2006
Místo konání: Praha 4, Budějovická 15
Kurzovné: 400,– Kč

211022 Kurz – Klinická biochemie stárnutí

Určeno pro pracovníky oboru klinické biochemie a klinické pracovníky se zájmem o danou problematiku.
Předběžný program: Teorie stárnutí, referenční hodnoty ve stáří, změny vnitřního prostředí, biochemie endokrinních změn, ovlivnění orgánových funkcí medikací, problematika intenzivní péče a laboratorního vyšetřování geriatrických nemocných, metabolická problematika výživy starších nemocných.
Vedoucí kurzu: prof. MUDr. A. Kazda, DrSc.
Termín konání: 13. 6. 2006
Místo konání: Praha 4, Budějovická 15
Kurzovné: 500,– Kč

(pokračování na s. 186)