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REVIEW ARTICLE

A review of HPRT and its emerging role in cancer

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Abstract
Hypoxanthine guanine phosphoribosyltransferase (HPRT) is a common salvage housekeeping gene with a historically important role in cancer as a mutational biomarker. As an established and well-known human reporter gene for the evaluation of mutational frequency corresponding to cancer development, HPRT is most commonly used to evaluate cancer risk within individuals and determine potential carcinogens. In addition to its use as a reporter gene, HPRT also has important functionality in the body in relation to purine regulation as demonstrated by Lesch–Nyhan patients whose lack of functional HPRT leads to significant purine overproduction and further neural complications. This regulatory role, in addition to an established connection between other salvage enzymes and cancer development, points to HPRT as an emerging influence in cancer. Recent work has shown that not only is the enzyme upregulated within malignant tumors, it also has significant surface localization within some cancer cells. With this is mind, HPRT has the potential to become a significant biomarker not only for the characterization of cancer, but also for its potential treatment.

Keywords Hypoxanthine guanine phosphoribosyltransferase (HPRT or HGPRT) · Lesch–Nyhan syndrome · Kelley–Seegmiller syndrome · Salvage enzymes

Nucleotide synthesis pathways

Nucleotides are an integral component of cellular life due to their versatility and abundance [1]. Their functional flexibility is demonstrated as ATP and GTP are utilized in both DNA and RNA synthesis and maintenance, while simultaneously acting as energy sources for the cell [2, 3]. Because the cell is reliant on its correct synthesis, the processes that regulate nucleotide production are tightly structured and controlled [4]. These mechanisms are responsible for maintaining adequate nucleotide levels at all times within the cell, which elevate as high as five- to tenfold increases during G1 and S phases of the cell cycle [5].

There are two distinct biological pathways that eukaryotic cells utilize to synthesize nucleotides: de novo synthesis and the salvage pathway. De novo synthesis is an energetically expensive 15-step process that requires up to 28 enzymes to synthesize nucleotides from raw materials within the cell [6]. The enzymes involved specifically in purine biosynthesis are responsible for converting organic glucose into phosphoribosyl pyrophosphate (PRPP), which can then be converted into GTP and ATP [7]. Because it requires extensive energy, this anabolic pathway is primarily used when the demand for nucleotides is the most prominent: during G1 and S phases [8]. Although complex in nature, this process is highly conserved between organisms, suggesting that it is ancient in origin [9].

The second mechanism, the salvage pathway, has several derived mechanisms that synthesize nucleotides from used materials within the cell [9]. While de novo synthesis creates the components of nucleotides, the salvage pathway utilizes a clever approach that 'recycles' parts from old nucleotides and pieces them together to form complete nucleotides. Due to the recycling nature of the salvage pathway, it is the chosen nucleotide synthesis mechanism throughout the cell cycle for both purines and pyrimidines as it aids in conserving valuable energy. Specifically, for purine synthesis, it is estimated that 90% of free purines in humans are recycled [10]. Therefore, the enzymes involved in this process are responsible for providing necessary purine nucleotides for DNA synthesis and maintenance.

Hypoxanthine guanine phosphoribosyltransferase (HPRT) is a salvage pathway enzyme responsible for the formation of

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IMP and GMP from precursors within the cell to eventually form inosine and guanine, respectively (Fig. 1) [11]. HPRT transfers phosphoribose from PRPP to hypoxanthine and guanine bases [10, 12]. The enzyme is composed of ten beta strands and six alpha helices with residues 37–189 forming the core of the enzyme [13]. Depending on the pH of the surrounding tissue, the protein can exist as either a dimer or a tetramer with identical subunits [13–15]. The molecular weight of each of the protein subunits is 48.9 kDa and the molecule has an instability index of 21.69, classifying the protein as stable. The functional homo tetramer contains four subunits labeled A, A′, B, and B′ (Fig. 2) [13].

The HPRT enzyme consists of several regions that each have distinct functions in substrate recognition and reactivity. The carboxy terminal end of the central beta sheet is primarily involved in substrate recognition. The core region of the protein contains twisted parallel beta sheets with five beta strands that are surrounded by four alpha helices.

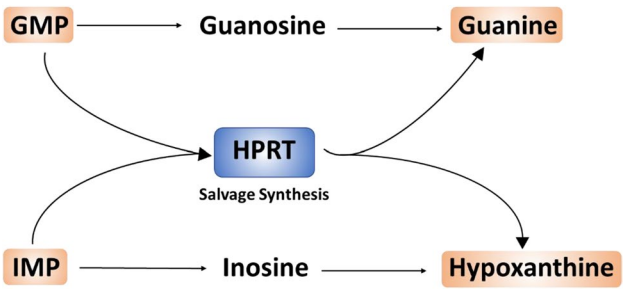

Fig. 1 An overview of the HPRT enzyme function. HPRT is responsible for the transfer of a ribose monophosphate from PRPP to hypoxanthine and guanine to form inosine monophosphate (IMP) and guanine monophosphate (GMP), respectively. Pyrophosphate is the byproduct from this reaction. After IMP and GMP are synthesized, they are converted to functional nucleotides used in DNA synthesis and repair

Residues 65–74 form the most flexible portion of the protein as they create a loop that will bind pyrophosphate. The residues of the enzyme that will bind PRPP substrate are 129–140, which are located on the floor of the active site. In order for enzymatic activity in the active site to be successful, the metal ion Mg^{2+} is required [13, 15].

The *hprt* locus

The *hprt* gene is 47,827 bp long and resides on the long arm of the X chromosome (Fig. 3). The gene is relatively large, especially considering that only a small portion of the transcribed DNA is eventually translated. There are nine exons that code for a 217-amino acid protein, which represents only 1.3% of the original genomic message [10, 16, 17]. Because the final protein product is involved in cellular maintenance, the control sequences upstream of the *hprt* gene contain the hallmarks of a mammalian housekeeping gene; there is an absence of 5′ transcriptional sequences including the TATA and CAAT boxes and there are exceptionally GC-rich sequences with many GC hexanucleotide motifs along the 5′ end of the gene [18]. As a housekeeping gene, *hprt* is found in all somatic tissue in low levels [19]. In a majority of human cells, *hprt* mRNA transcripts comprise only 0.005–0.01% of the total mRNA within the cell [20]. The only exception is in central nervous tissue where there is an unusually elevated level of HPRT expression ranging from 0.02 to 0.04% of the total mRNA, which is a fourfold increase in comparison to other somatic tissue [20, 21]. This elevated expression is not fully understood because cells in the central nervous system (CNS) are not stimulated to divide and would therefore require less machinery for nucleotide synthesis. In addition, the human genome contains non-functional HPRT homologous regions in the

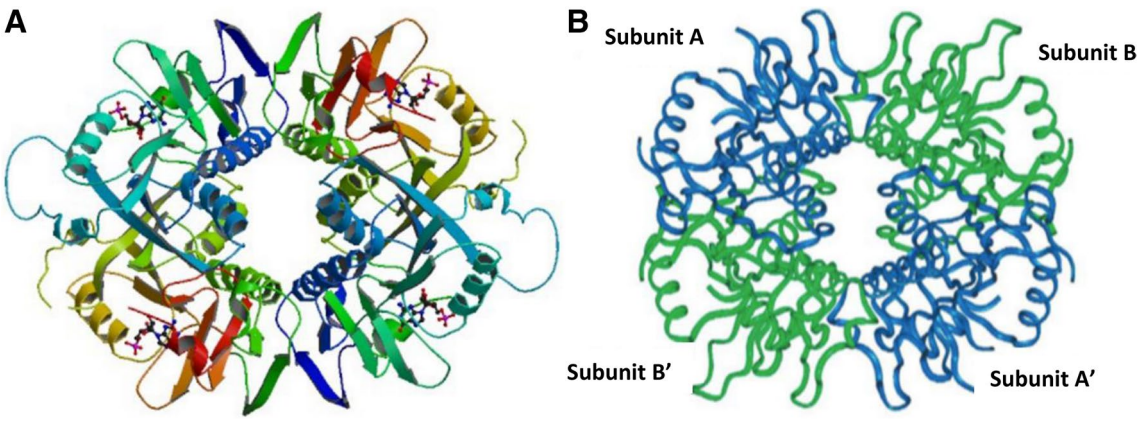

Fig. 2 HPRT protein structure. The homo tetramer structure of human HPRT. **a** The protein consists of only 27% alpha helices and 27% beta sheets, which indicates that the remaining 46% of the enzyme consists of beta turns and random coils. **b** Individual subunit labeling is indicated by the altering colors. Each subunit is identical and is translated from the same mRNA message

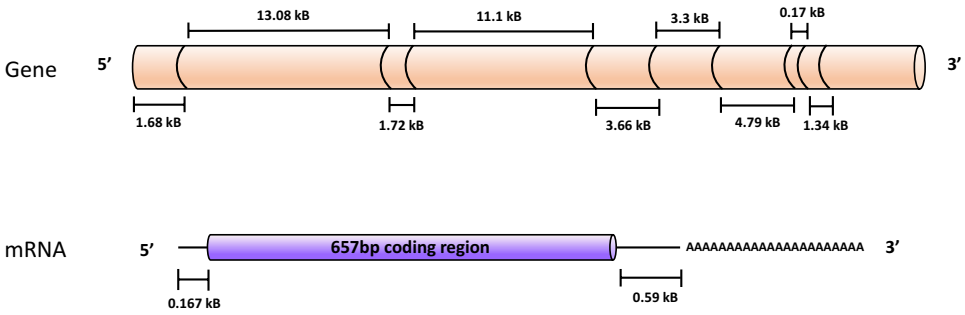

Fig. 3 The HPRT locus. The HPRT gene contains nine exons coding for a 657-bp coding mRNA and a resulting 217-amino acid protein

autosomal DNA of chromosomes 5, 11, and 13 [16]. These DNA sequences are not known to be transcribed and are most likely pseudogenes, but their exact origin and expression are not well understood [22].

HPRT regulatory role: examples from Lesch–Nyhan syndrome

As an essential housekeeping protein, a deficiency of HPRT results in a spectrum of diseases that directly correspond with the availability of the protein. Individuals with a complete lack of functional HPRT develop Lesch–Nyhan syndrome, while individuals with a partial deficiency develop gout-like symptoms characteristic of Kelley–Seegmiller syndrome [21]. Because the gene is located on the X chromosome, it is an X-linked recessive condition that predominantly affects males of diseased families. A common thread that connects these distinct diseases is the presence of hyperuricemia in patients. The excess of uric acid within the plasma, usually ranging between 9 and 12 g per liter, contributes to many of the underlying symptoms typical of HPRT deficiency [22]. These symptoms are not present in individuals who are deficient in any of the other salvage pathway enzymes despite having the same function in nucleotide synthesis.

Lesch–Nyhan syndrome is primarily characterized by severe neurological illnesses. Patients suffer from dystonia, choreoathetosis, twisting and writhing, akathisia, akinesia, and several other motor neuron disorders that make successful voluntary motion incredibly difficult and frequently impossible. Along with motor neuron dysfunction, patients also suffer from severe self-injurious behavior that can lead to self-mutilation [22–28]. Along with improper neural development, Lesch–Nyhan patients also show significant purine overproduction. This overproduction indicates that HPRT is crucial in not only the synthesis of purines, but also the regulation of their production [21].

When patients have a reduced level of HPRT rather than a complete deficiency, they develop gout-like manifestations and eventual gouty arthritis, distinctive of Kelley–Seegmiller syndrome [21]. Partial HPRT deficiency usually develops from a point mutation resulting in a single amino acid substitution within the protein [22]. Many such mutants have been characterized and are often present in the amino-terminal domain of the protein [27]. These mutations generally stay within family lineages, and it is rare that two separate families share the same mutation. Symptoms are directly related to, and caused by, the excess production of uric acid within the body. Diseased individuals pass large amounts of urate crystals into the urine for a majority of their early life, and after approximately 20 years of chronic hyperuricemia an inflammatory response develops that leads to arthritis [17]. In Lesch–Nyhan syndrome and Kelley–Seegmiller syndrome, the regulatory nature of HPRT is demonstrated as the lack of the protein results in an overproduction of purines. We suggest a possible negative feedback loop controlling purine production that may be regulated by the availability of HPRT within the cell: as cells have sufficient purines, HPRT is utilized to halt further purine synthesis.

Relationship between other salvage pathway enzymes and cancer

Involved in the same salvage pathway, nucleotide synthesis pathway as HPRT, Thymidine Kinase 1 (TK1), previously known as fetal TK, is an enzyme that controls pyrimidine synthesis of thymine. TK1 catalyzes the conversion of thymidine to deoxythymidine monophosphate (dTMP) [29]. Due to its presence in the serum of cancer patients, TK1 is known as a proliferative biomarker in cancer development and as a biomarker to monitor recurrence [30–35]. The serum detection of TK1 is an early step in cancer growth and has been used as an early detection system for cancer prevention as elevated serum levels have been shown to correspond with tumor aggressiveness [30, 36–38]. It has also been suggested that TK1 could be used to distinguish between slowly growing tumors and more aggressive, fast-growing tumors [39]. In addition, TK1 has been established as a cancer biomarker for multiple cancers including leukemia, colorectal cancer, lung cancer, breast cancer, and prostate cancers [37, 40]. As an established biomarker for cancer development,

TK1 demonstrates the relationship between cancer proliferation and the control of salvage enzymes.

HPRT as a reporter gene

The role HPRT has played within the realm of cancer has been largely limited to its use as an established human reporter gene. The *hprt* gene is currently used to assess somatic mutations and mutagenesis in in vitro and in vivo studies evaluating potential carcinogens and cancer therapies [41–45]. As the first human somatic gene mutation assay developed, the HPRT assay has been thoroughly used to identify and select mutant cells by taking advantage of the biochemical pathways used to synthesize DNA within cells [46–48]. Mutations in the *hprt* locus are carefully monitored in studies of individuals exposed to both potential mutagens and carcinogenic agents to determine the effects of exposure to DNA integrity and resulting cancer risk [49–53]. Using this mutational biomarker, researchers have found significant correlations between HPRT mutations and increased cancer risk [45, 50, 52–58]. Gladd and Tindall used the *hprt* locus to determine the mutation rate of various cancer cell lines with mismatch repair-gene defects [59], while Branda et al. utilized the *hprt* locus to monitor the DNA mutation rate of women with breast cancer treated with tamoxifen, radiotherapy, or chemotherapy [54]. As such an influential biomarker for cancer development, the utilization of *hprt* has led to significant contributions to the cancer community.

Emerging role in cancer

Recently, new evidence has indicated an emerging role for HPRT within cancer. Researchers have found that HPRT has elevated expression specifically within cancer cells. Muller et al., using quantitative PCR, found that HPRT was present in breast cancer cell lines (MDA-MB-231), primary tumors, and tumor-infiltrated lungs of SCID mice injected with MDA-MB-231 breast cancer cells. Yet, they found no detectable amount of the enzyme in normal lungs from healthy mouse counterparts. Additionally, Muller et al. found that the mRNA levels of *hprt* directly correlated with the tumor load of the tested mouse, indicating that the level of HPRT within the mouse was related to the size of the tumor [60]. Furthermore, the evaluation of HPRT expression in cancer patients via immunohistochemistry shows significant variability between cancer patients [61]. Overall, HPRT is generally overexpressed within cancer patients as data from both tissue and RNA-seq show significant increases in protein levels within malignant samples [61]. While there is an overall increase in malignancy, HPRT overexpression is not a consistent trend within all patients, and only a cohort of cancer patients experience an upregulation [61]. This indicates that the regulation of HPRT synthesis is compromised within those patients. As previously discussed, HPRT has a regulatory function within the cell that may contribute to this apparent lack of transcriptional control within malignant cells. As a protein with differential expression, HPRT has the potential to be used as a characterization tool when assessing patient tumors and evaluating treatment options.

In addition to showing unique expression profiles within malignant tumors, HPRT also has been implicated as a possible surface biomarker. Recent work has shown that HPRT co-localizes with the plasma membrane of certain cancer cell lines [62]. As a potential cancer-associated antigen, HPRT could become a target for emerging immunotherapies designed to attack cancer cells displaying unique surface proteins. As the expression of the enzyme is generally consistent and extremely low within normal cells, HPRT could become a useful tool for those patients who experience an upregulation. We propose that HPRT is involved in some regulatory pathway monitoring and controlling nucleotide synthesis and protein production, and within a malignant environment this regulation is lost and HPRT becomes overexpressed allowing cancer cells to bypass pathways controlled or regulated by strict HPRT production. Further work is required to solidify HPRT as a significant biomarker for cancer identification, characterization, and possible targeting, but the enzyme has recently shown significant promise as not only a mutational reporter gene, but also a cancer biomarker and neoantigen.

Compliance with ethical standards

Conflict of interest All the authors declare that they have no conflict of interest.

Research involving human and animal participants This article does not contain any studies with animals performed by any of the authors.

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