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Biomarkers for Mechanistic Studies: HPRT Mutation

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Abstract

The human germinal mutations in the X-chromosomal gene for Hypoxanthine-guanine Phosphoribosyl Transferase (HPRT) quickly made it a useful target for research of somatic mutations in vitro and in vivo in humans and animals. HPRT functions as a basic reporter gene in this manner. For obvious reasons, the in vivo mutational research have focused on peripheral blood cells. Humans exposed to environmental mutagens are currently monitored using in vivo mutations in T cells, with investigations of molecular mutational spectra serving as adjuncts to identifying the cause. HPRT mutations have been found to have unexpected clonality among TCR gene-defined T cell clones in vivo, suggesting that HPRT mutations could be probes for fundamental cellular and biological processes. The use of HPRT in this way has allowed researchers to look at recombinase-mediated mutations as markers of a carcinogenic mutational process, use somatic mutations as surrogate markers for in vivo T cell proliferation that underpins immunological processes, and discover and study mutator phenotypes in non-malignant T cells. The role of HPRT in this last application is related to its function as well as its utility as a mutation reporter. HPRT is now being used in studies of *in vivo* selection for in vivo mutations that arise in somatic or germinal cells.

Keywords: HPRT mutations; Biomarker; Humans; Genomic instability; Lesch-Nyhan syndrome

Introduction

The human HPRT narrative began with a publication in "Science" over 30 years ago, which reported an enzyme deficiency connected to sex-linked human brain disease and excessive purine metabolism. The Lesch–Nyhan syndrome, named after its discoverers, is a catastrophic clinical illness characterised by neurological, mental, arthritic, and metabolic impairments, including significant urate overproduction. Fortunately, it is uncommon, and the symptoms are now recognised as being of varying degrees of severity. The Hypoxanthine-guanine Phosphoribosyl Transferase (HPRT) gene was the X-linked gene described in this early publication. These early studies focused on germline HPRT mutations and how they manifested themselves in the affected males who inherited them. HPRT was significant for its function rather than its value as a reporter. Because these newly discovered mutations conferred a distinct cellular as well as clinical phenotype, somatic cell genetics benefited almost immediately [1]. The phosphoribosylation of hypoxanthine and guanine, which saves them for nucleic acid production, requires HPRT enzyme activity. Purine analogues (e.g. 8-azaguanine, 6-thioguanine, and 6-mercaptopurine) are also phosphoribosylated, which is required for their cytotoxicity. HPRT mutant cells benefit from resistance to these analogues because it acts as a highly efficient selective system, allowing them to thrive while wild-type cells are killed. HPRT mutant cells, on the other hand, are reliant on de novo purine biosynthesis for nucleic acid synthesis since they lack the salvage pathway. As a result, they are extremely sensitive to one-carbon transfer inhibitors, killing them in quantities that would kill wild-type cells [2]. The HAT (hypoxanthine, aminopterin, and thymine) reverse selection system is based on this. HPRT is currently an important part of the arsenal of genetic markers used in animal and human cell in vitro mutagenesis investigations. In humans, it is a single copy gene located at location Xq. The enzyme's amino acid sequence and the HPRT coding region's nucleotide sequence (654 bp) are both known [3]. The gene in genomic DNA is around 44 kb long, with nine short exons and eight considerably longer introns, and it has been sequenced in its entirety. On chromosomes, there are four non-functional HPRT pseudogenes. The fact that this gene, which is so commonly used in mutation research, came to our attention through human germinal mutations is crucial to my storey. Why utilise HPRT mutations for human biomonitoring if they aren't sensitive measurements of genotoxic chemical exposure? Mutations are impact biomarkers, meaning they reflect genotoxicity *in vivo* [4]. Increases in HPRT MF coupled with known mutagenic exposures suggest that the exposure is

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affecting the environment being studied. Genotoxicity in humans exposed to a chemical that is known to be a genotoxic carcinogen in animals adds to the weight of evidence that the agent is also carcinogenic in humans, making this endpoint more important for determining cancer risk. *In vivo*, HPRT mutations or suppression can show the efficiency of chemoprevention programmes aimed at protecting against the mutagenic effects of a specific environment or cancer treatment, or establishing "safe" levels of exposure to recognised genotoxic chemicals. Finally, HPRT mutations can be utilised as exposure indicators when no other biomarker is available or, in rare cases, to identify a specific exposure. The latter, on the other hand, necessitates the identification of molecular mutational spectra [5].

Conclusion

The storey began with somatic cell genetics, progressed to mutagenicity monitoring, and finally took advantage of molecular genetics' new technology. HPRT mutations have proven to be valuable probes for elucidating processes underlying both the mutagenesis process and immune responses. *In vivo* evolution of genomic instability has also been documented in HPRT mutant T cell populations, which may not be confined to malignant cells but may be a fundamental feature of all cells. The one downer is that we learned about this amazing target gene and its mutations through the Lesch-Nyhan syndrome, a horrible human heritable disease. Perhaps a partial pay-back will be our use of this target gene to prevent a rise in affected persons or, better yet, to convince ourselves that such an increase will not occur.

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