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Review

Low-Molecular-Weight Protein Tyrosine Phosphatase and Human Disease: in Search of Biochemical Mechanisms

NUNZIO BOTTINI[1], EGIDIO BOTTINI[2], FULVIA GLORIA-BOTTINI[3] and TOMAS MUSTELIN[1]*

[1] Program of Signal Transduction, La Jolla Cancer Research Center, The Burnham Institute, 10901 North Torrey Pines Road, La Jolla, CA 92037, USA, [2] Department of Neurosciences, [3] Department of Biopathology, University of Rome Tor Vergata, Rome, Italy

Abstract. A major challenge in the post-genomic era is to identify the physiological functions of genes and elucidate the molecular basis for human disease. Genetic polymorphisms offer a convenient avenue for these efforts by providing evidence for the involvement of a given gene in human pathophysiology. Here we review the current evidence linking the low-molecular-weight protein tyrosine phosphatase (LMPTP) to several common diseases, including allergy, asthma, obesity, myocardial hypertrophy, and Alzheimer's disease. Based on the known effects of the genetic polymorphisms on the alternative mRNA splicing and enzyme levels of LMPTP, we discuss the possible molecular mechanisms of LMPTP involvement in these diseases.

Key words: tyrosine phosphatase; genetic polymorphisms; allergy; asthma; obesity.

Introduction

Rapid progress has been made in our understanding of human diseases at the molecular level during the last decades. Finding the responsible gene is often of great value for the subsequent development of targeted treatments, which can even be curative. In most cases, the scientific discovery process has followed the path "human disease-biochemical abnormalities-gene responsible". In recent years, the application of modern molecular biology and the elucidation of the human genome have also generated numerous genes "in search of a disease". In these cases, the function of the gene and its protein product have to be determined before their relevance for pathogenesis of human diseases can be addressed through a variety of experimental approaches, notably genetic animal models. An alternative approach, which is currently gaining momentum, is the analysis of gene polymorphisms and their correlation with human pathophysiology.

This paper will discuss the case of the low-molecular-weight protein tyrosine phosphatase (LMPTP), also known as acid phosphatase 1 (ACP1), which is encoded by a gene with well-recognized polymorphisms that correlate with a remarkable variety of medical conditions[7]. Despite this relevance for pathophysiology, the biochemical function and role of LMPTP has remained obscure. In essence, LMPTP is a "disease-related gene in search of its biochemical mechanisms".

Abbreviations used: ACP1 – acid phosphatase 1, ADA – adenosine deaminase, FMN – flavin mononucleotide, G6PD – glucose-6--phosphate dehydrogenase, LMPTP – low-molecular-weight protein tyrosine phosphatase, SNP – single nucleotide polymorphism.

*Correspondence to: Prof. Tomas Mustelin, M.D. Ph.D., Program of Signal Transduction, La Jolla Cancer Research Center, The Burnham Institute, 10901 North Torrey Pines Road, La Jolla, CA 92037, USA, tel.: +1 858 713 6270, fax: +1 858 713 6274, e-mail: tmustelin@burnham-inst.org

From Acid Phosphatase to Protein Tyrosine Phosphatase

LMPTP was originally isolated as an acid phosphatase from red blood cells[27, 36]. It was also found to be present at high concentrations in many other tissues[35]. The enzyme resolved by non-denaturing starch gel electrophoresis into two isoforms[35], called fast (F) and slow (S), or A and B. Both isoforms are small enzymes consisting of only 157 amino acid residues and with a molecular weight of 18 kDa. The two isoforms have been isolated from several species, and a high degree of conservation in the primary structure is evident in eukaryotes from yeast and fruit flies to humans[48, 51, 56]. Surprisingly, several enzymes with high similarity to LMPTP have also been isolated from prokaryotes[33]. This unusually high degree of conservation through evolution suggests that the enzyme is responsible for some fundamental function common to all cells.

The ACP1 gene that encodes LMPTP is located on chromosome 2p25 and spans 7 exons and 6 introns[17]. The amino acid sequence of LMPTP[25, 77] revealed that the two isoforms are encoded by a single gene and arise through a pre-mRNA splicing process, in which either exon 3 or 4 is excised and the other retained[24, 38]. Thus, the two isoforms are identical to each other outside the 40-amino acid region, called the variable loop, which is encoded by exon 4 in the S isoform and by exon 3 in the F isoform. Both isoforms are N-terminally processed by the removal of Met-1 and the addition of an acetyl group to Ala-2[25]. More recently, additional LMPTP isoforms have been discovered, including the smaller, catalytically inactive protein derived from the excision of both exons 3 and 4[74], and the non-productive use of cryptic slice sites[64, 49].

In the mid-1980s it was found that LMPTP readily dephosphorylates phosphotyrosine, but not phosphoserine or phosphothreonine[18]. For this reason, the enzyme was reclassified from a nonspecific acid phosphatase to a protein tyrosine phosphatase. Indeed, the crystal structure of LMPTP[73, 78] clearly demonstrated that LMPTP has the same catalytic machinery[20, 73, 78, 79] and core structure as other protein tyrosine phosphatases[54]. On the primary sequence level, however, LMPTP is quite different from other protein tyrosine phosphatases and probably does not share a common ancestor with them[54]. For historical reasons, particularly because of the change in its perceived substrate specificity, LMPTP is known by many additional names in the literature, including cytosolic low molecular weight protein tyrosine phosphatase (cLMWPTPase[12] or LMW-PTP[60]), human adipocyte acid phosphatase (hAAPα and hAAPβ for the two isoforms[67]), human cytosolic low-molecular-weight protein tyrosine phosphatase A and B (HCPTPA and HCPTPB[37]), and bovine heart protein tyrosine phosphatase (BPTP[80]). The human gene has retained the designation ACP1.

Polymorphism of the ACP1 Gene

The polymorphism of ACP1 was initially discovered at the protein level by HOPKINSON et al.[36], who described six different patterns on starch gel electrophoresis of hemolysates. These authors attributed these patterns to the combination of three codominant alleles at the ACP1 autosomal locus. The three ACP1 alleles have been sequenced[66] and found to be based on three single-nucleotide polymorphisms (SNPs) that affect both the total enzymatic activity and the ratio[23] between the F and S isoforms in a characteristic manner, thus explaining the different patterns seen in starch gel electrophoresis. Fixed combinations of these SNPs define the common genotypes *A, *B and *C (Table 1). In the *A allele, amino acid 105 is an arginine residue (codon CGA), while it is a glutamine (codon CAA) in *B and *C. The two other SNPs do not change the encoded amino acid residues, but strongly affect the alternative mRNA splicing and, as a result, the ratio between the two isoforms: F/S is 2:1 in *A, 4:1 in *B, and 1:4 in *C. The total enzymatic activity, measured with p-nitrophenylphosphate as a substrate, is in the order *A/*A < *A/*B < (*B/*B, *A/*C) < *B/*C < *C/*C[1]. Additional rare alleles have also been described, including a low-activity allele, termed *GUA, found in the Guaymi Indian population of Panama and Costa Rica[50]. A null ACP1 allele has also been described[23]. No ho-

Table 1. The three common ACP1 alleles and their SNPs

Allele	Codon 43	Codon 44	Codon 105	Ratio of F/S[1]
*A	GA**T** (Asp)	AG**C** (Ser)	C**G**A (Arg)	2:1
*B	GA**C** (Asp)	AG**C** (Ser)	C**A**A (Gln)	4:1
*C	GA**C** (Asp)	AG**T** (Ser)	C**A**A (Gln)	1:4

[1] The total enzymatic activity, measured with p-nitrophenylphosphate as a substrate, is in the order: *A/*A < *A/*B < (*B/*B, *A/*C)< <*B/*C < *C/*C.

mozygotes for this allele have been reported, perhaps only due to its very low frequency.

Physiological Function of LMPTP

Despite the detailed understanding of the ACP1 locus that encodes the LMPTP isozymes and the crystal structure of the enzyme, as well as numerous biochemical investigations, the physiological function of LMPTP remains unknown. The variable loop encoded by exon 3 or 4 forms one side of the catalytic pocket and, not surprisingly, the two isoforms show different substrate preferences, kinetics and allosteric properties *in vitro*[21, 26, 71]. Thus, it is very likely that the two isoforms have, at least partly, different substrates and functions in intact cells.

The discovery that LMPTP can dephosphorylate phosphotyrosine prompted many investigators to ask if LMPTP regulates signaling pathways that involve tyrosine phosphorylation. Indeed, overexpressed LMPTP can counteract the malignant transformation by tyrosine kinase oncogenes[62, 65] as well as signaling by growth factor receptors[2, 19, 61, 72]. Our laboratory has found that LMPTP dephosphorylates a negative regulatory phosphorylation site in the ZAP-70 tyrosine kinase in T cells[16]. This event leads to increased activation of this kinase and enhanced signaling from the T cell antigen receptor. LMPTP can also be phosphorylated on tyrosine itself[63, 75], a modification that appears to activate the enzyme.

In red blood cells, where LMPTP is abundant, it has been suggested to dephosphorylate the erythrocyte membrane protein band III[3]. This integral membrane protein is phosphorylated by the Lyn and Syk tyrosine kinases, a modification that leads to reduced binding of several peripheral membrane proteins[39], including the metabolic enzymes phosphofructokinase, aldolase, glyceraldeyde-3-phosphate-dehydrogenase and catalase, and elevated glycolytic rates[34]. Dephosphorylation by LMPTP would be expected to have the opposite effect. At least *in vitro*, the F isoform seems to have a higher affinity than the S isoform for phosphopeptides derived from the band III[71]. However, it remains uncertain if band III is a physiologically relevant substrate for LMPTP in intact red blood cells.

Is LMPTP Really a Tyrosine Phosphatase *in Vivo*?

The observation that LMPTP can dephosphorylate phosphotyrosine in the test tube and can affect tyrosine phosphorylation in intact cells when overexpressed does not necessarily mean that LMPTP acts solely as a protein tyrosine phosphatase in intact cells. *In vitro*, the two LMPTP isoforms are also active against flavin mononucleotide (FMN), dephosphorylating it to riboflavin[28]. In Chinese hamster ovary cell extracts, LMPTP constitutes most of the intracellular FMN phosphatase activity[28]. If this is a true function in intact cells, LMPTP may be important for respiration and the anti-oxidant defense of cells by the regulation of the levels of FMN (and flavin adenine dinucleotide) available for a broad range of flavin nucleotide-dependent enzymes, including glutathione reductase. In support of this notion, human subjects carrying the rare *GUA allele also have increased glutathione reductase activity in their red blood cells[50]. It has also been observed that cells transfected with LMPTP have a reduced glutathione reductase activity[47].

LMPTP in Human Pathophysiology

In the following sections, we will review the role of ACP1 polymorphism in the etiology or modulation of the clinical pictures of several human diseases, ranging from hemolytic favism to Alzheimer's disease. We will also discuss the possible mechanisms of how LMPTP may be involved as either a protein tyrosine phosphatase or a flavin mononucleotide phosphatase.

Acute hemolytic favism

Subjects with a deficit of glucose-6-phosphate dehydrogenase (G6PD) of Mediterranean type may have severe episodes of hemolytic favism, a disease characterized by an acute idiosyncratic hemolytic response to molecules derived from fava beans (*Vicia faba*). It has been calculated that only about 30% of enzymopenic subjects have one or more episodes during their life, pointing to the presence of other genetic factors contributing to these severe hemolytic manifestations.

An association between hemolytic favism and LMPTP genotype in male subjects with G6PD deficiency from the population of Sardinia and Rome was reported by one of us in 1971[9]. The order of susceptibility to favism is (*A/*A; *A/*C) > (*A/*B, *B/*C) > *B/*B, which provides a significant negative correlation between the disease and the concentration of F isozyme[8]. The concentration of S isoform does not appear to be correlated with susceptibility to favism.

The high level of expression of LMPTP in erythrocytes, the target cells in hemolytic favism, supports the

notion of a direct link between LMPTP genotype and the molecular mechanism of hemolysis. A possible substrate for LMPTP in erythrocytes is the integral membrane protein band III, as discussed above. Increased phosphorylation of this protein due to low LMPTP levels would be expected to decrease binding of metabolic enzymes and decrease the rate of glycolysis. Increased phosphorylation may also alter the interaction of band III with other proteins, the distribution of band III in the erythrocyte membrane, and the plasticity of the erythrocyte. In individuals with low levels of F isozyme, these effects could contribute to enhancing the effects of toxins from *Vicia faba*, resulting in a lower threshold for hemolysis in G6PD deficient subjects[8].

The acute hemolysis characteristic of favism resembles that seen in response to antimalarial drugs and other agents causing oxidative stress in individuals with G6PD deficiency of Black type. In the absence of this enzyme, the production of NADPH via the pentose phosphate pathway, which in erythrocytes is the only available route, is severely reduced. NADPH, in turn, is required for glutathione reductase, which converts oxidized glutathione to reduced glutathione, which is important for maintaining function and stability of hemoglobin and other proteins. In G6PD deficiency, NADPH production is insufficient to withstand oxidative stress and hemoglobin is oxidized to methemoglobin, which aggregates and disturbs the integrity of the erythrocyte, rendering it sensitive to destruction. In favism, the response to toxins from *Vicia faba* is quite similar to that seen after chloroquine in Black subjects with G6PD deficiency. The possible function of LMPTP as an FMN phosphatase may also impact on the same general homeostasis of hemoglobin and other proteins, although the mechanism is not immediately obvious. An effect of LMPTP on glutathione reductase activity has been observed in cells transfected with exogenous LMPTP[47].

Malaria

The notion that LMPTP plays a physiological role in erythrocytes is also supported by the significant negative correlation between LMPTP S isoform levels and resistance to malaria[58]. Studies on populations in Sardinia, who were subjected in the past to a heavy malaria burden, show a lower concentration of the S isoform compared with a nearby malaria-free population, suggesting that genotypes with high S isoform concentration have been subjected to negative selection in a malaria environment. Glucose-6-phosphate dehydrogenase deficiency also protects against malaria. However, correlation analysis demonstrates that the relationship between past endemic malaria and the S isoform was not mediated by G6PD deficiency[11].

The biochemical mechanism(s) by which LMPTP modulates malaria[4, 11] may be related to those involved in favism. Infection of erythrocytes by *Plasmodium falciparum* involves a conformational change in band III[55], which is accompanied by the exposure of adhesine, thus contributing to the cytoadherent properties of infected red blood cells. The phosphorylation state of band III may affect this process. In subjects carrying the *C allele, the high concentration of S isoform may decrease phosphorylation status of band III, leading to decreased resistance to invasion by the parasite. Dephosphorylation of FMN by LMPTP may also play a role, as suggested by the resistance to malaria infection in subjects that lack G6PD. Apparently, a reduced resistance to oxidative stress is beneficial for preventing malaria infection[11].

Rheumatoid arthritis

In a recent, unpublished survey on a sample of patients with rheumatoid arthritis, we observed that the frequency of the *C allele, which is associated with a high concentration of the S isoform, was significantly higher than in controls. *C/*C homozygotes were found at an unusually high frequency as compared with the control population.

The etiopathology of rheumatoid arthritis is complex, and it is unclear what cell type LMPTP polymorphisms may affect in this disease. A simple possibility would be that a high level of the S isoform predisposes T lymphocytes to autoreactivity, as has been proposed for other protein tyrosine phosphatases[52, 53]. This possibility is supported by our observation that the S isoform of LMPTP can dephosphorylate a negative regulatory site, Tyr-292, in the ZAP-70 kinase, leading to its hyperactivation[16]. Thus, individuals with high S isoform levels may have T cells in which T cell antigen receptor ligation leads to an exaggerated or prolonged T cell response to viral or other antigens that eventually trigger the synovial inflammation that characterizes rheumatoid arthritis.

Allergy and asthma

The correlation between ACP1 genotypes and serum IgE levels were studied in England[14] and Italy (BOTTINI et al., submitted). In the former study, 150 subjects with atopic asthma and 150 local population

control subjects were compared. In the latter study, 124 children were recruited in a prospective study on asthma and atopy. In both studies, the mean value of serum IgE was lower among subjects carrying the *B/*C genotype than in other ACP1 genotypes. The *B/*C genotype carries the highest total LMPTP enzymatic activity, suggesting that one or both LMPTP isoforms exert an inhibitory role in a pathway relevant for IgE hyperproduction.

Genotyping of 118 children with bronchial asthma in Rome (unpublished) showed a correlation of ACP1 allele and the age at onset of symptoms. In particular, females with low-activity LMPTP genotypes showed the highest risk of bronchial asthma after the first year of life as compared with males and females with high--activity genotypes (O. R.=2.8 $p<0.01$).

Taken together, these studies suggest that LMPTP plays a significant role in the susceptibility to allergy and asthma. This role may relate to the function of LMPTP in IgE-producing B cells or helper type 2 T cells[52, 53]. Altered mast cell function in subjects with low LMPTP activity could also contribute.

Inflammatory bowel diseases

ACP1 genotypes having high levels of F isoform correlate positively with incidence of Crohn's disease in females ($p<0.02$) and ulcerative colitis in males ($p<0.03$)[12]. These autoimmune conditions involve multiple cytokines and growth factors, most of which utilize tyrosine phosphorylation for signaling. The F isoform of LMPTP may affect one or several of these signaling pathways or, directly, the function of autoreactive lymphocytes in the mucosa.

Diabetes mellitus and obesity

In two large studies (n=276 and n=214), the proportion of *A allele was lower and the concentration of F isoform was higher in nonobese non-insulin-dependent diabetic patients with high blood glucose levels (mean value greater than 8.9 mmol/l) than in nonobese diabetic patients with a low blood glucose levels[29, 40]. No significant association was observed in obese subjects. Two studies on insulin-dependent pediatric diabetes (n=189) and adolescent diabetes (n=86) showed that disease onset was significantly earlier in females with medium to high total LMPTP activity compared with males[15].

LMPTP is also a highly significant predictor[42] of diabetic retinopathy ($p=0.005$). A significant interaction with adenosine deaminase (ADA) genetic polymorphism has been observed. Diabetic subjects (n=276) carrying the ACP1*B/*B genotype and the ADA*2 allele have the highest proportion of retinopathy (26.1%), while non-*B/*B subjects carrying the ADA*2 allele have the lowest proportion (3.7%).

ACP1 genotypes *A/*A and *B/*A, which result in the lowest levels of total LMPTP activity, are significantly higher in severely obese, nondiabetic individuals[10, 41, 43, 57]. In another study[13], the *A allele was found to be negatively associated with the levels of total cholesterol ($p=0.002$) and triglycerides ($p<0.001$) in 154 obese Caucasian subjects in the United States. A highly significant correlation between the concentration of F isoform and triglycerides level was observed.

The pattern of association between the LMPTP genetic polymorphism and clinical variability of obesity suggests a multipoint action of this ubiquitous phosphatase. Its expression in adipocytes suggests that LMPTP may affect the behavior of these cells in a genotype-dependent manner. A function as FMN phosphatase and regulator of overall rate of respiration and metabolism could explain at least some of these observations. Dephosphorylation of the insulin receptor[19] is another possibility.

Cardiology

Familial hypertrophic cardiomyopathy is an autosomal dominant disease caused by mutations in genes encoding for sarcomeric proteins[46]. Many different mutations have been found in different families affected by the disease and a striking variability in clinical picture is present even among members of the same families carrying the same mutations. Particularly the age of onset and the degree of left ventricular hypertrophy seem to be influenced by environmental factors and by other genes.

Two independent studies[7, 44] have shown that *C allele carriers have a higher incidence of hypertrophic cardiomyopathy. A highly significant linear relationship between the maximum wall thickness and the amount of total LMPTP activity has also been observed[44]. This positive correlation between the degree of hypertrophy and LMPTP activity indicates that the hypertrophic response of the myocardial wall is positively modulated by LMPTP. This response involves several growth factors[45], including platelet-derived growth factor, insulin, and insulin-like growth factor 1. The receptors for all of these have been reported to be regulated by LMPTP[2, 19, 71]. Alternatively, LMPTP levels may determine the rate of respiration and overall metabolism by converting FMN to riboflavin. Thus,

high LMPTP activity could result in lower metabolic rate and a stronger need for a hypertrophic response.

Neurology

LMPTP is well expressed in brain and is enriched in nerve endings[76]. A reduced activity of LMPTP in Alzheimer's disease brains was described by SHIMOHAMA et al.[69]. It was later shown that the reduced LMPTP activity was due to reduced LMPTP protein levels[68] and not to a reduction in specific activity in the affected brains. The phosphorylated EGF receptor has been proposed as a physiological substrate for LMPTP in the brain[70], as has the tau protein, the phosphorylation of which is involved in the pathogenesis of Alzheimer's disease[59].

In a recent study[22], 142 brain samples from 42 early-onset Alzheimer's disease patients and 100 late--onset Alzheimer's disease patients, with postmortem--confirmed diagnoses, were genotyped for the *A/not*A polymorphism. 181 age-matched subjects were considered as controls. There was a significant association of the low-activity *A allele with disease (p=0.0016), particularly the early-onset type (p=0.00008), and somewhat less with late-onset disease (p=0.013). These genotyping results agree with the earlier biochemical findings, and together they suggest that low total LMPTP activity predisposes to Alzheimer's disease.

Intrauterine and early neonatal development

In a study[32] on 173 women with a history of two or more repeated spontaneous abortions (RSA), we observed that the proportion of carriers of the *C allele was lower than in normal pregnant women and in other control groups. Women with RSA show a specific decrease of LMPTP S isoform concentration as compared with normal pregnant women. The data suggest that women with LMPTP genotypes showing a high concentration of S isoform are less prone to spontaneous abortion.

In another RSA study[6], we analyzed the ratio of wife vs. husband ACP1 activity and, in healthy puerpera that of mother vs. infant. The results indicated that when LMPTP activity is lower in the mother than in her fetus, the probability of abortion is higher and the survival to term is lower. In contrast, when LMPTP activity is higher in the mother than in her fetus, the probability of abortion is lower and the survival to term is higher. Further analysis indicated that the effect is due to the S isoform, i.e. a high mother-to-child S isoform ratio favors intrauterine survival.

In a study on 609 consecutively newborn infants in Rome[1], it was observed that LMPTP phenotypes with the lowest activity (*A/*A and *A/*B) showed a clear tendency to higher rates of intrauterine growth. Phenotypes with the highest activity (*B/*C and *C/*C) show a tendency towards mean values, while individuals of *B/*B and *A/*C phenotypes (intermediate LMPTP activity) show a high proportion of both extreme birth weight values. These patterns of relations between birth weight and LMPTP genotype are statistically significant only in males.

The pattern of appearance of serum haptoglobin during the first few days after birth is considered as an indicator of perinatal development. ACP1 genotypes with the lowest F isoform concentration show the highest rate of haptoglobin development during the early neonatal period, while the *B/*B genotype having the highest F isoform concentration shows the lowest rate of haptoglobin development (n=299; p=0.05).

Taken together, these studies support a role for LMPTP activity in the regulation of embryogenesis and intrauterine growth rate. This role could be mediated by either tyrosine phosphatase activity, which may modulate growth hormone signaling, or FMN phosphatase activity, which may control the rate of cell respiration and metabolic activity. Genetic differences in the activity of LMPTP between the maternal and the fetal parts of the placenta may also be important in the development and survival of the zygote in the uterus. Differential signaling or metabolic rates on each side of the placenta may lead to an imbalance between nutrient supply and demand.

Fertility

A more intriguing correlation is that between ACP1 genotype and season of conception. Two studies[30, 31] involving 329 and 361 newborns, respectively, demonstrated that the total activity of LMPTP shows a minimum in infants conceived in January and February and a maximum in those conceived towards the end of the calendar year. This effect may relate to a role of LMPTP in cell respiration and metabolic rate.

Concluding Remarks

The biochemical basis varies enormously in complexity from disease to disease. While some conditions are caused by a dominant or recessive inheritance of mutations in single genes that lead to easily understood biochemical abnormalities, most diseases are multifac-

torial with a complex pattern of inherited and environmental causes. It is generally believed that the susceptibilities to and clinical pictures of many common diseases are largely determined by the combination of several predisposing gene alleles, which individually show a weak correlation, but together synergize to affect pathogenesis or repair and recovery processes to a highly significant extent. The identification of genetic polymorphisms provides a basis for studying these genetic interactions. In parallel with the improvement of the data on the human genome, a large number of human genes have been found to contain SNPs. However, in most cases these SNPs are not yet known to affect the expression of the genes or the function of the encoded proteins. The ACP1 gene is a striking exception to this rule, and it is clear that the studies of its polymorphism have been both informative and stimulating.

Although the biochemical basis for the role of LMPTP in human pathophysiology remains to be elucidated, a number of helpful conclusions can be drawn from the studies on ACP1 genotypes in human disease. First, LMPTP is clearly of physiological relevance for the normal functioning of red blood cells, for the immune system, for lipid storage in adipocytes, for neurons, as well as for other cell types. Second, the two isoforms of LMPTP appear to have distinct biological functions. Generally, high levels of total LMPTP activity seem to reduce cellular metabolic rates, protect against conditions such as allergy, asthma and abortion, and reduce blood lipid levels, but they also appear to increase blood sugar levels, to reduce haptoglobin production and promote pathological hypertrophy of the myocardium. Low levels of LMPTP activity correlate with obesity, perhaps through increased cell metabolism and storage in adipocytes. Low LMPTP in the brain may also favor storage and the development of Alzheimer's disease. Differences have been observed specifically in relation to the concentration of F and S isoforms. Third, LMPTP must be involved in an important regulatory process, since the relatively modest differences in expression levels between alleles are sufficient to affect pathogenesis in a statistically significant manner in whole populations.

Finally, given the genetic evidence for the involvement of LMPTP in several prevalent human diseases (Table 2), we believe that this enzyme should also be vigorously pursued as a drug target. This notion is supported by the observation that relatively modest variations in total LMPTP activity or isozyme ratio is sufficient to predispose for, or protect from, several human afflictions. A specific inhibitor for LMPTP would be able to cause more significant changes in activity and could, therefore, have very beneficial effects in the treatment of rheumatoid arthritis and other inflammatory or autoimmune diseases. Conversely, a small molecule that mimics the allosteric activation of the F isoform by hypoxanthine or the S isoform by adenine (which inhibits F) would be beneficial for asthma, obesity and Alzheimer's disease.

Table 2. Summary of ACP1 disease associations

Condition	Predisposition[1]
Acute hemolytic favism	medium-low F levels
Malaria	high S levels
Rheumatoid arthritis	high S levels
High serum IgE	medium-low total activity
Bronchial asthma	low total activity
Inflammatory bowel disease	high F levels
Glycemic level in NIDDM	medium-high total activity
Severe obesity (nondiabetic)	low total activity
High blood lipids	medium-high total activity
High birth weight	low total activity
Spontaneous abortion	medium-low total activity
Slow development of haptoglobin in neonates	high F levels
Hypertrophic cardiomyopathy	high total activity
Alzheimer's disease	low total activity

[1] Positive correlation with disease.

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