FOCUS ON RESEARCH

Mevalonate Kinase Deficiency and Autoinflammatory Disorders

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Related article, page 2700

A deficiency of mevalonate kinase resulting in mevalonic aciduria was the first inherited defect in cholesterol and nonsterol isoprene biosynthesis to be recognized.[1] Nine other enzyme deficiencies have since been identified in the distal part of the cholesterol biosynthesis pathway. They are associated mainly with skeletal and organ malformations, skin abnormalities, and psychomotor retardation. Recently, two defects in the synthesis of coenzyme Q10 (also called ubiquinone) have been associated with disorders that clinically resemble abnormalities of mitochondrial energy metabolism.

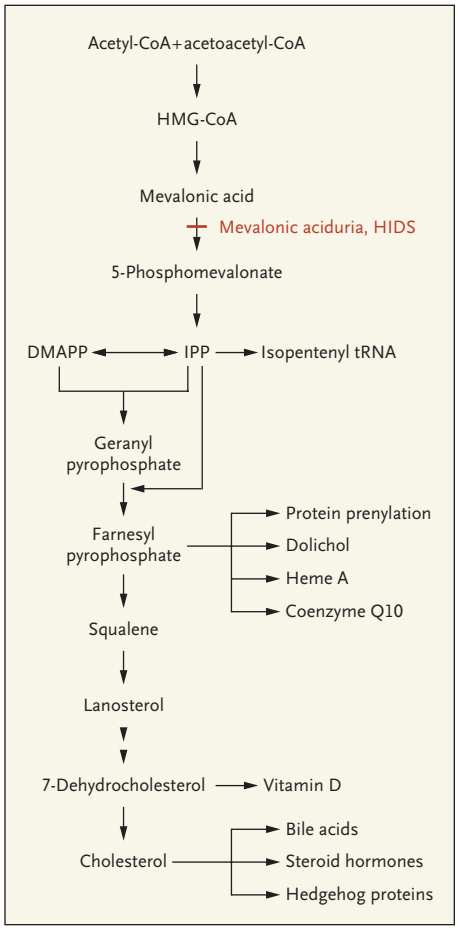
The clinical manifestations of mevalonic aciduria are diverse.[2] Severely affected patients present from birth with failure to thrive, microcephaly, dysmorphic features, and neurologic involvement, including psychomotor retardation, cerebellar atrophy, ataxia, and progressive myopathy. A periodic fever syndrome with hepatosplenomegaly, lymphadenopathy, arthralgia, and rashes dominates the clinical picture from infancy. During the febrile episodes, the erythrocyte sedimentation rate, blood leukocyte counts, serum C-reactive protein levels, IgD and IgA1 levels, and urinary leukotriene excretion are greatly increased. Severe polyarthritis and ocular involvement with retinal dystrophy and cataracts develop in some patients. Mevalonate kinase deficiency also causes the hyperimmunoglobulinemia D syndrome (HIDS), an autoinflammatory periodic fever syndrome that is not associated with perinatal abnormalities and has fewer neurologic manifestations than mevalonic aciduria. Both disorders are allelic and attributable to recessive mutations in the mevalonate kinase gene (*MVK*) located on chromosome 12q24. The more severe clinical presentation of mevalonic aciduria appears to correlate with the lowest level of residual mevalonate kinase activity.[3]

The primary product of mevalonate metabolism is cholesterol, which is further converted into steroid hormones and bile acids (see figure). Mevalonic acid is also the first committed intermediate in the synthesis of dolichols, which act as carriers in the assembly of carbohydrate chains of glycoproteins; coenzyme Q10, which participates in electron transport; isopentenylated transfer RNAs (important for protein synthesis); and prenylated proteins, which are involved in intracellular signal transduction. Isoprenylation of proteins is critical for the function of cellular proteins related to growth control and the cell cycle, including the proto-oncogene *ras*. Regulation of the pathway is maintained through a multilevel feedback system that employs transcriptional and post-translational controls.

Despite a lack of residual mevalonate kinase activity in cultured cells from affected patients, plasma levels of cholesterol lipoprotein, apolipoproteins, steroid hormones, and primary bile acids are normal in most patients. This paradox is related to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and the low-density lipoprotein (LDL) cholesterol receptor, which are key regulatory sites in the cholesterol pathway. In cultured skin fibroblasts from patients with mevalonic aciduria, the activities of HMG-CoA reductase and LDL cholesterol receptors are up-regulated, apparently as compensatory responses that ensure sufficient production of mevalonic acid and thus almost normal function of the pathway.

The biosynthesis of coenzyme Q10, by contrast, is decreased in patients' fibroblasts, and there are decreased levels of coenzyme Q10 in plasma. These findings suggest that farnesyl pyrophosphate, an important intermediate at the branch point between sterol and isoprenoid biosynthesis, is shuttled toward cholesterol synthesis at the expense of isoprene biosynthesis.

The cause of the inflammatory attacks is unclear. Mevalonic aciduria and HIDS trigger a dominance of type 2 helper T cells (Th2), resulting in elevated levels of interleukins 4, 5, and 6, tumor necrosis factor α (TNF-α), and immunoglobulins (hyper-IgD



Pathway of Cholesterol and Nonsterol Isoprenoid Biosynthesis.

A deficiency of mevalonate kinase resulting in mevalonic aciduria and HIDS is indicated by a red bar. CoA denotes coenzyme A, HMG 3-hydroxy-3-methylglutaryl, DMAPP dimethylallyl pyrophosphate, IPP isopentenyl pyrophosphate, and tRNA transfer RNA.

or hyper-IgE). Potential mechanisms by which mevalonate kinase deficiency might induce a Th2 bias may reside within cell-signaling proteins and lipid rafts — assemblages of cholesterol and sphingolipids in the lipid bilayer. Recently, a link was shown between apoptosis and aberrant isoprenylation of proteins involved in cell-cycle regulation: the apoptosis that statin-induced mevalonate depletion induces in cultured cells could be inhibited with the addition of farnesyl diphosphate or geranylgeranyl diphosphate, both of which are cell-permeable isoprenoid analogues.[4]

Urinary excretion of leukotriene (LT) E_4 is elevated in most patients with mevalonic aciduria, and there is a positive linear correlation between this elevation and increased excretion of mevalonic acid. Increased urinary LTE_4 excretion suggests that there is increased total systemic cysteinyl leukotriene synthesis.[5] The cysteinyl leukotrienes — LTC_4, LTD_4, and LTE_4 — are lipid mediators that are generated in the 5-lipoxygenase pathway from arachidonic acid. The cysteinyl leukotrienes are believed to increase vascular permeability through the contraction of endothelial cells, which results in edema and hemoconcentration.

Various treatments have been used for HIDS with variable success; in patients with mevalonic aciduria, the attacks can be influenced only marginally, and the overall prognosis remains poor. Direct replacement of the end product (coenzyme Q10 or cholesterol) has failed to control the syndrome. Corticosteroid treatment is effective in diminishing the severity of attacks but cannot prevent crises. The use of statins resulted in further clinical decompensation in two patients with mevalonic aciduria but reduced the frequency and severity of fever attacks in patients with HIDS. Several patients have benefited from treatment with interleukin-1–receptor antagonists (e.g., anakinra) or TNF-α inhibitors (etanercept), but the success of these approaches has been limited in patients with mevalonic aciduria.

In this issue of the *Journal*, Neven and colleagues (pages 2700–2703) report the positive results of allogeneic bone marrow transplantation in a boy with mevalonic aciduria and severe, life-threatening, and uncontrollable inflammatory attacks. This report documents a courageous clinical approach whose success will trigger studies on the links between autoinflammatory, rheumatic, and allergic disorders and the cholesterol and isoprenoid pathway.

The rationale for attempting bone marrow transplantation in this boy with an almost unmanageable periodic fever syndrome was that it might correct immune function. Successful donor lymphohematopoietic engraftment resulted in a clear decrease in inflammatory cytokines, a reduction in mevalonate excretion, and most important, a cessation of febrile attacks. The marked enlargement of the liver and the spleen resolved after the procedure, indicating that the hepatosplenomegaly was an effect of extramedullary hematopoiesis rather than a primary process in those organs.

Although the results reported by Neven et al. are encouraging, and bone marrow transplantation may become an important therapeutic option for patients

with mevalonic aciduria who have primarily inflammatory disease, important questions remain. Since the excretion of mevalonate derived from extramedullary sources remained high after the transplantation, it will be most important to know whether further neurologic disease, such as cerebellar atrophy or myopathy, develops. Concentrations of coenzyme Q10 and other isoprenoid derivatives may not increase sufficiently in other body tissues.

Mevalonic aciduria and HIDS are rare disorders, but they represent a unique link among inborn errors of metabolism, side effects of statin therapy, and inflammatory and rheumatic disorders. Bone marrow transplantation will help elucidate the pathophysiology of this constellation of disorders, as well as others involving similar immunologic abnormalities, including the Wiskott–Aldrich syndrome (elevated IgA and IgE levels and increased rate of infections), Omenn's syndrome (elevated IgE levels), the hyper-IgE syndrome, and more common rheumatic and allergic disorders.

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