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The Battlefield of Rare Diseases: Where Uncommon Insights Are Common

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Evolution requires imperfect fidelity of replication, that is mutations, and these mistakes ultimately reveal the exquisite functionality of Nature. The rare diseases that populate our species represent the manifestations of Nature's errors. Rare though they are, their study has revealed important insights about normal physiology that in turn have provided a better understanding of common disorders, universal mechanisms, critical pathways, and therapies that are useful for treating more than one disease.

In the United States, a rare disease is defined by the 1983 Orphan Drug Act as one that affects fewer than 200,000 people. Such disorders comprise the bulk of maladies addressed by the Undiagnosed Diseases Program of the National Institutes of Health (NIH), which was established in 2008 (<http://rarediseases.info.nih.gov/Resources.aspx?PageID=31>). This program has two principal goals: to reach an accurate diagnosis for patients with unknown and undiagnosed disorders and to discover new diseases that provide insights into human physiology, biochemistry, and genetics. Rare diseases identified through the NIH Undiagnosed Diseases Program and similar initiatives will be topics for discussion at a symposium in Vienna, Austria that will also address how to translate the science of rare diseases into the care of patients with these disorders (<http://dmm.aaas.org/>).

That translation is perhaps best illustrated by the classic work of Goldstein and Brown on the role of the low-density lipoprotein (LDL) receptor in cholesterol homeostasis. Their group efforts emanated from investigations into an extremely rare genetic defect, familial hypercholesterolemia, a fatal disorder of cholesterol metabolism caused by mutations in the gene encoding the LDL receptor. Not only did this basic research give rise to an understanding of the role of the LDL receptor in regulating cholesterol synthesis, it also provided paradigm-changing insights into the importance of cholesterol in the development of atherosclerosis and, later, to the use of statins to inhibit cholesterol synthesis and decrease the risk of coronary artery disease.

Alkaptonuria provides another example of how the study of rare diseases has yielded information of value for treating more common disorders. Recognized by Garrod as the first inborn error of metabolism in the early 20th century, this autosomal recessive disease manifests with darkening and destruction of connective tissues (ochronosis) (1). Patients suffer vertebral disc narrowing and calcification beginning in their fourth decade, with deterioration of large joints and cardiac valves a decade later. In alkaptonuria, genetic deficiency of homogentisic acid (HGA) dioxygenase in the tyrosine degradative pathway causes accumulation of HGA, which oxidizes to form benzoquinones that polymerize and

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react with bone and joint tissue. Knowledge of this defect and dissection of the tyrosine catabolic pathway, have led to the medical use of nitisinone, a potent inhibitor of the second step in tyrosine catabolism, which is catalyzed by para-hydroxyphenylpyruvic acid dioxygenase, the enzyme that produces HGA. Nitisinone is currently the treatment of choice for the rare fatal hepatic disease, tyrosinemia type I, due to deficiency of fumarylacetoacetate hydrolase, which acts downstream of HGA; hepatic failure results from the accumulation of reactive oxygen species. Nitisinone reduces flux through the tyrosine catabolic pathway sufficiently to rescue children with tyrosinemia type I from developing liver disease. Moreover, nitisinone prevents HGA accumulation, producing a potential “cure” for alkaptonuria. The most striking application of nitisinone, however, involves a side effect, that of hypertyrosinemia. Increased plasma and cellular tyrosine concentrations have the potential to stabilize and provide more substrate for tyrosinase, the enzyme catalyzing the rate-limiting step in melanin pigment production. This could have enormous benefit for individuals with oculocutaneous albinism characterized by reduced pigment formation and ophthalmic involvement, specifically nystagmus and impaired visual acuity. If those patients have residual amounts of tyrosinase activity, nitisinone treatment could result in increased pigment in the hair, skin, and, most critically, in the eyes, where the retinal pigment epithelium nourishes the rod and cone photoreceptor cells required for vision (2). Indeed, nitisinone treatment has the potential to improve the development of vision in infants with mild oculocutaneous albinism. In addition, other patients with deficiencies of melanin production could have their pigmentation enhanced by nitisinone treatment.

Then there is cysteamine, the current therapy for the lysosomal storage disease cystinosis. In cystinosis, the disulfide cystine accumulates to 50 to 100 times normal concentrations in cellular lysosomes because of a genetic deficiency in cystinosin, the lysosomal membrane protein that transports cystine out of lysosomes. Affected individuals develop renal tubular Fanconi syndrome in the first year of life, manifest growth retardation and glomerular failure by 10 years of age, and experience a variety of nonrenal complications after renal transplant. Cysteamine, or beta-mercaptoethylamine, passes through the plasma membrane and lysosomal membrane to interact with cystine in a disulfide interchange reaction, producing cysteine and cysteine-cysteamine mixed disulfide, both of which can leave the cystinotic lysosome via transporters that are not defective in cystinosis. The resulting cystine depletion has salutary effects on renal function, growth, and virtually all of the late complications of the disease (3). Now, cysteamine's good safety profile and efficacy in the rare disease cystinosis have prompted its investigational use in two common diseases, nonalcoholic steatohepatitis and Parkinson's disease. These uses of cysteamine are based upon its antioxidant properties, as cysteamine enhances production of the reducing agent glutathione.

Another rare and illustrative monogenic disorder is Hereditary Inclusion Body Myopathy, or GNE myopathy. This late-onset, quadriceps-sparing myopathy results from biallelic mutations in GNE, the gene that encodes UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase. This bifunctional enzyme catalyzes the initial, rate-limiting steps in sialic acid synthesis. Sialic acid serves as the terminal, charged sugar of N-linked and O-linked glycoproteins, which are essential for cell-cell interactions and for a variety of other functions. In GNE myopathy, sialic acid deficiency causes hyposialylation of selected glycoproteins, including the muscle glycoprotein α -dystroglycan, resulting in symptoms of myopathy. Knowledge of the sialic acid synthetic defect in GNE myopathy has led to treatment strategies involving the administration of N-acetylmannosamine (ManNAc, an intermediate in the sialic acid synthetic pathway distal to the genetic defect in GNE myopathy) (4). ManNAc enhances sialic acid production and restores glycoprotein sialylation. However, sialic acid depletion causes more than muscle disease; it is also associated with defective renal function, because the glomerular foot processes rely upon

sialylated glycoproteins for filtration. Hence, ManNAc is now being considered as a treatment for some fairly common kidney diseases, and it could find applications in a host of other disorders involving impaired sialylation.

One fairly common disease, idiopathic pulmonary fibrosis, affects approximately 40,000 individuals in the United States; two-thirds are over 60 years of age, and only 25% survive for 5 years after diagnosis. The disorder has heterogeneous etiologies and no effective treatment. A rare disease called Hermansky-Pudlak Syndrome (HPS), however, could help investigators to parse out the causative factors in idiopathic pulmonary fibrosis. Of the nine known genetic subtypes of HPS, all characterized by oculocutaneous albinism and bleeding due to platelet defects, only three (HPS-1, HPS-2, and HPS-4) also cause pulmonary fibrosis. The interstitial lung disease of HPS starts at approximately 30 years of age and results in death about 10 years after the onset of symptoms. All of the HPS subtypes occur because of genetic defects in the machinery that forms and traffics lysosome-related organelles; that machinery consists of protein complexes called BLOCs (Biogenesis of Lysosome-related Organelle Complexes) or adaptors (specifically, adaptor complex-3, or AP-3). Elucidation of the mechanism by which aberrant intracellular trafficking causes interstitial lung disease in HPS could reveal the primary pathway responsible for more generalized fibrotic diseases.

Last, consider a disease of lower extremity vascular calcification and claudication (pain due to vascular insufficiency) called Arterial Calcification due to Deficiency of CD73 or ACDC, which affects only nine patients in the world (5). In this autosomal recessive disorder, mutations in the *NT5E* gene result in deficiency of its product, CD73. This enzyme converts adenosine monophosphate to adenosine and inorganic phosphate on the surface of vascular endothelial cells. Ordinarily, the adenosine produced by CD73 binds to receptors that signal inside endothelial cells to suppress tissue nonspecific alkaline phosphatase (TNAP). In ACDC, however, TNAP production fails to be trophically inhibited by adenosine, and elevated concentrations degrade matrix pyrophosphate to inorganic phosphate. Given that matrix pyrophosphate inhibits mineralization and that inorganic phosphate enhances it, vascular calcification occurs. Treatment could be provided in the form of bisphosphonates, drugs designed to prevent osteoporosis, which inhibit TNAP. The discovery of ACDC and its pathogenesis has revealed a previously unknown role for adenosine in vascular calcification, stimulating further investigations into its role in atherosclerosis, bone formation, Monckeberg's medial calcific sclerosis, and ectopic calcification in general.

Indeed, ACDC represents just one example of the many rare disorders now being described by harnessing the power of genome-wide single-nucleotide polymorphism and whole exome sequencing analyses, combined with the extensive phenotyping provided by programs such as the NIH Undiagnosed Diseases Program. Evolution invested eons in creating systems of biology that function at the highest levels. Now, we are increasingly defining disruptions in those systems, perpetrated by genetic mutations and expressed in the form of rare diseases. As a result, rare disease research is revealing Nature's secrets, held for millennia, with unexpected benefits.

Biography

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