ognized. While the authors' findings on experimental infections of laboratory mice may not change opinions on appropriate antibiotic therapy for patients, they point to testable hypotheses on the mechanisms for lingering illness after treatment of infection (18, 19) and laboratory means to identify persistent antigenic and mitogenic stimulation.

With PCR and sensitive antigen detection methods so readily at hand, we may neglect more direct but time-consuming and artful gauges of viability. Almost 50 years ago, Gutman, Turck, Petersdorf, and Wedgwood reported in the *JCI* the survival of bacterial variants in antibiotic-treated patients with pyelonephritis (20). They used painstaking methods in a pre-PCR microbiology lab for "separation of bacterial variants from classical organisms." These remains in the urine were uncultivable by routine procedures but, according to the authors, lived to cause disease again.

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What's in a name?

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Mutations in numerous genes encoding ribosomal proteins (RPs) occur in 50%–70% of individuals with Diamond-Blackfan anemia (DBA), establishing the disease as a ribosomopathy. As described in this issue of *JCI*, Sankaran, Gazda, and colleagues used genome-wide exome sequencing to study DBA patients with no detectable mutations in RP genes. They identified two unrelated pedigrees in which the disease is associated with mutations in *GATA1*, which encodes an essential hematopoietic transcription factor with no known mechanistic links to ribosomes. These findings ignite an interesting and potentially emotional debate on how we define DBA and whether the term should be restricted to pure ribosomopathies. More generally, the work reflects the powerful knowledge and controversies arising from the deluge of data generated by new genetic technologies that are being used to analyze human diseases.

The history of DBA

In 1938, pediatricians Louis Diamond and Kenneth Blackfan described a congenital anemia with hypoplasia of red blood cell precursors and concomitant congenital extrahematopoietic anomalies in about one-third of patients (1). The etiology of this syndrome, now known as Diamond-Blackfan anemia (DBA), has fascinated and perplexed pediatric hematologists for many years. In 1997, Dahl and colleagues identified a child with DBA and a X:19 chromosomal translocation, linking a critical region of chromosome 19 to DBA in a proportion of multiplex families (2). Positional cloning revealed that the mutated gene was *RPS19*, which encodes a protein component of the small 40S ribosomal subunit (3). Subsequently, *RPS19* mutations were identified in approximately 25% of DBA families, all of which showed dominant inheritance. Speculation about how *RPS19* mutations might cause DBA ensued for about 10 years. Specifically, it was debated as to whether the disease results from loss of unique extraribosomal activities of RPS19 or through impaired ribosome production. Support for the latter hypothesis emerged when a flurry of other DBA genes were identified, all of which encoded different small or large ribosomal subunit proteins (RPs) (4).

DBA perceived as a ribosomopathy

Currently, 50%–70% of DBA patients are accounted for by mutations in one of

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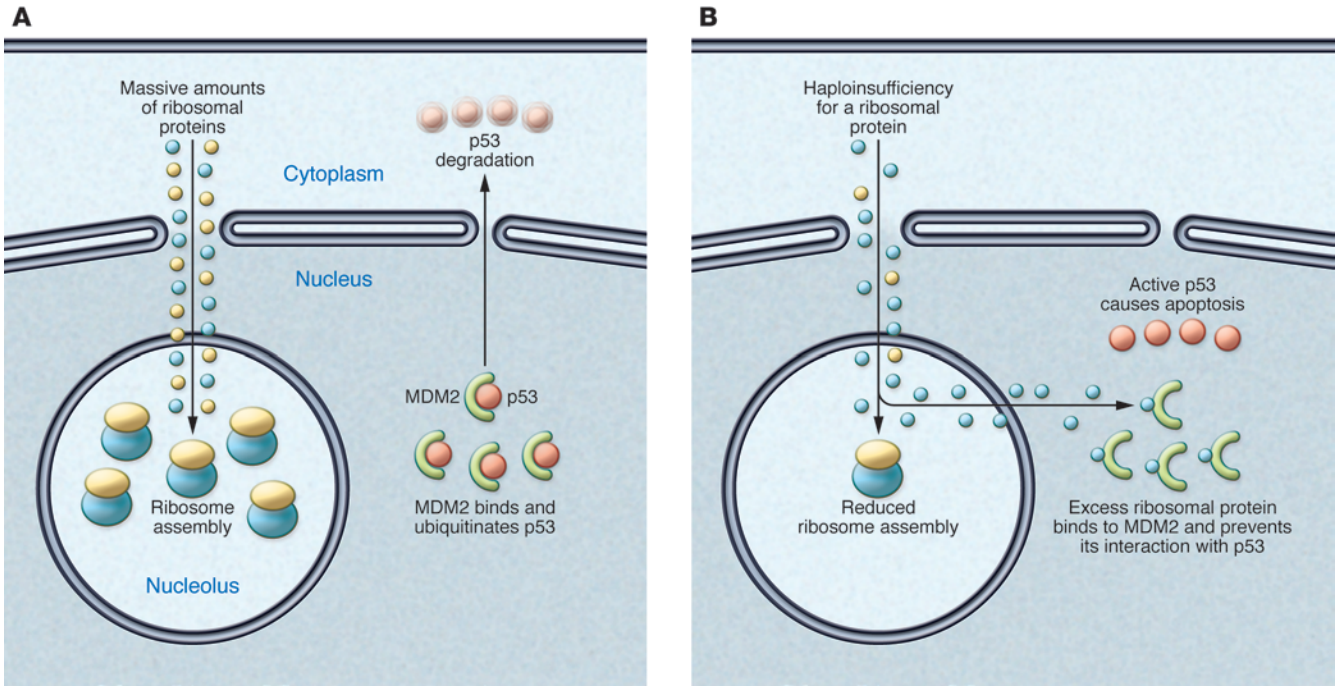

Figure 1
Current model for how RP haploinsufficiency causes DBA. (**A**) Normal erythroblasts produce large numbers of ribosomes for protein synthesis. Levels of p53 remain low via a feedback loop whereby MDM2, a transcriptional p53 target, ubiquitinates p53 to promote its degradation by proteasomes. (**B**) Haploinsufficiency for specific RPs causes accumulation of other RPs, which bind to MDM2, thereby inhibiting its ability to promote p53 degradation. Consequently, p53 accumulates and triggers cell cycle arrest and apoptosis.

10 RP genes (4, 5). Additional diseases in which causative mutations impair ribosomes include the inherited Treacher-Collins and Shwachman-Diamond syndromes and 5q- myelodysplastic syndrome, caused by a somatic chromosomal deletion (4). These disorders illustrate the concept that genetic alterations in basic cellular pathways can produce unique combinations of organ-specific pathologies. How ribosome disruptions lead to DBA is not understood, but a popular theory is that imbalances in individual RPs trigger a p53-mediated checkpoint leading to cell cycle arrest and apoptosis of erythroid precursors (4). In support, certain RPs bind to and inhibit the p53 regulator MDM2 (6). Moreover, in animal models, the DBA-like effects of RP mutations depend in part on p53 (refs. 7, 8, and Figure 1).

GATA1 gene mutations in patients diagnosed with DBA

Sankaran and colleagues used genome-wide exome sequencing to analyze most or all transcribed genes in two brothers without an apparent mutation in any RP gene (9). Both patients harbored a mutation in the X chromosome–encoded *GATA1* gene. By targeted sequencing of an additional 62 male DBA patients, all negative for RP gene mutations, they identified a second family with an independent *GATA1* gene mutation. Both of these mutations alter mRNA splicing to favor the production of an amino-truncated GATA-1 protein termed GATA-1 short, or GATA-1s.

GATA-1, a zinc finger transcription factor expressed mainly in blood cell precursors, is essential for the development of red blood cells, megakaryocytes and their platelet progeny, mast cells, and eosinophils (10). Several human blood disorders are caused by *GATA1* mutations that partially reduce and/or alter function of the corresponding protein (ref. 11 and Figure 2). Germline mis-

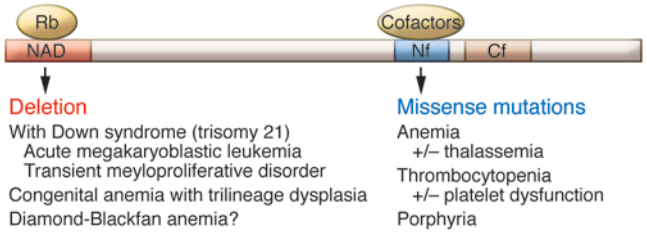

Figure 2
GATA1 mutations associated with human disease. The diagram indicates GATA-1 protein with functional modules including the NH_2-terminal activation domain (NAD), amino zinc finger (Nf), and carboxyl zinc finger (Cf). The NAD physically interacts with the retinoblastoma protein (Rb), which may modulate the ability of GATA-1 to regulate cell division and/or survival. Loss of the NAD through somatically acquired splice, frameshift, or nonsense mutations causes myeloproliferative disorder and leukemia in young children with Down syndrome (trisomy 21). In the absence of Down syndrome, germline mutations resulting in loss of the NAD are associated with congenital anemia. Different surfaces of the Nf interact with DNA (nor shown) and protein cofactors including FOG1 and SCL/TAL1. Missense mutations that alter these interaction surfaces of the Nf cause inherited anemia and/or thrombocytopenia with other abnormalities, as indicated.

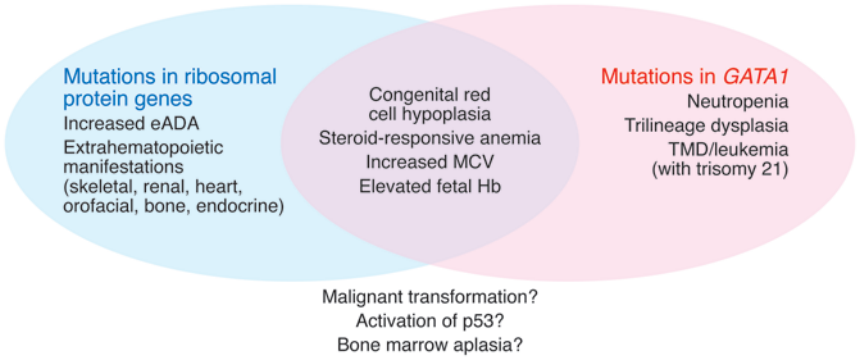

Figure 3
Shared and distinct phenotypes in congenital red cell aplasia caused by mutations in RP genes and in *GATA1*. eADA, erythrocyte adenosine deaminase activity, MCV, mean corpuscular volume; Hb, hemoglobin; TMD, transient myeloproliferative disorder.

sense mutations that alter the amino-terminal (NH_2) zinc finger motif of GATA-1 protein can impair DNA binding and/or cofactor interactions. Clinical phenotypes associated with such mutations include anemia and/or thrombocytopenia, platelet dysfunction, porphyria (disrupted heme synthesis), and thalassemia (imbalanced globin chain synthesis). Another class of clinically important *GATA1* mutations occur in exon 2 or surrounding introns and lead to the production of GATA-1s, which lacks amino acids 1–83. This region is termed the NH_2-terminal activation domain (NAD), by virtue of its ability to activate transcription in non-erythroid cells. The NAD binds the retinoblastoma tumor suppressor protein, which may regulate the capacity of GATA-1 to control cell survival or proliferation (12). Somatic mutations leading to the predominant production of GATA-1s are invariably associated with transient myeloproliferative disorder (a preleukemia) and acute megakaryoblastic leukemia in young children with Down syndrome (10). Sankaran et al. (9) identified two different DBA-associated germline *GATA1* mutations, both at the end of exon 2. These mutations alter mRNA splicing to favor GATA-1s production. While not formally proven, it is highly likely that the anemia in these patients is caused by *GATA1* mutations. Complicating matters, one of the mutations was described previously in a Brazilian pedigree with affected males exhibiting congenital anemia, neutropenia, and trilineage dysplasia of blood precursors (13). These patients were not diagnosed with DBA, although their clinical features overlapped with those of the patients described by Sankaran et al.

The controversy

While DBA is phenotypically and genetically heterogeneous, a pathogenic mutation in an RP subunit gene usually consolidates the clinical diagnosis. In individuals without RP gene mutations, the diagnosis is based purely on clinical findings after a variety of other conditions that cause erythroid hypoplasia are excluded (14). The patients described by Sankaran et al. received their clinical diagnosis from DBA experts according to current consensus guidelines. Moreover, mutations in *GATA1* and RP genes clearly produce overlapping phenotypes (Figure 3). These findings raise the question of whether *GATA1* should be included as a new "DBA gene." Alternatively, should *GATA1* gene mutations be excluded before a clinical diagnosis of DBA is made? Both views have their justifications, shortcomings, and precedence in the nomenclature of human disease. Suddenly becoming "not DBA" or a "different type of DBA" through new genetic testing can unsettle patients and physicians when a diagnosis that they have come to accept potentially unravels.

Medical syndromes are typically defined by signature constellations of physical and laboratory findings. Most were named years ago according to clinical features (e.g., dyskeratosis congenita) or after physicians who first described them (e.g., DBA or Fanconi anemia [FA]). More recently, molecular studies have revealed that many of these syndromes are genetically heterogeneous, with causative mutations occurring in one of multiple genes that function in a common pathway, thereby explaining the shared clinical phenotype. For example, FA, a bone marrow failure syndrome characterized by hypoplasia of all blood cell precursors (aplastic anemia), cancer predisposition, and abnormalities in organogenesis, is caused by mutations in at least 15 distinct genes that interact to sense and repair DNA cross-links (15). Indeed, verifying that candidate proteins function in this DNA repair pathway has strengthened the identification of new FA genes. Analogously, it is predicted that new DBA genes will somehow participate in ribosome biology. This raises the interesting question of whether ribosomes and GATA-1 are functionally linked. Both DBA and loss of GATA-1 induce apoptosis of erythroid precursors (16, 17). Through direct and indirect transcriptional actions, GATA-1 inhibits the expression of proapoptotic proteins and promotes the expression of antiapoptotic ones (18). Moreover GATA-1 binds p53 directly to inhibit its apoptotic activities (19). Thus, GATA-1 and ribosome biosynthesis may intersect through their abilities to control erythroid apoptotic regulators. In addition, ribosome dysfunction could selectively affect the translation of specific mRNAs, altering the proteome with particularly deleterious consequences in erythroid cells. Through this mechanism, it is possible that mutations in RP subunit genes somehow impair the expression of GATA-1 and/or its cofactors. Alternatively, it is possible that GATA-1 and ribosome functions are not directly linked and that two independent pathways cause the same phenotype. Other inherited disorders, for example hereditary deafness, retinitis pigmentosa, and VACTERL/VATER association, are genetically heterogeneous, each with causative mutations in genes affecting diverse functional pathways. Complicating the issue, similar or identical *GATA1* mutations can produce varying clinical manifestations in different individuals (Figure 3), explaining in part why the patients described by Sankaran et al. were diagnosed with DBA, whereas the family described by Hollanda et al. carries the diagnosis of "congenital anemia with trilineage dysplasia" (13).

What's in a name?

Categorizing inherited disorders according to conventional nomenclature provides rich historical perspective and an important contextual framework in which to classify clinical phenotypes. However, it is now obvious that one "disease" as defined clinically can have multiple genetic etiologies with unique implications for prognosis and medical management. For example, identification of an X-linked causal

mutation for congenital red cell aplasia or "DBA" in the current study provides important information for genetic counseling of affected families. Clearly, how we name diseases is less important than how we understand them. As diagnostic DNA sequencing becomes increasingly convenient and less expensive, it is more important than ever for practicing physicians to be aware of the clinical consequences of individual gene mutations, the limitations of current knowledge, and the fast-moving new insights that come our way with the advancing technologies of gene discovery.

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Lighting the fat furnace without SFRP5

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WNT signaling plays a central role in the regulation of cellular growth and differentiation. In this issue of the *JCI*, Mori et al. link WNT signaling to the oxidative capacity of adipocytes during obesity. They show that secreted frizzled-related protein 5 is an extracellular matrix–residing protein that is highly induced during obesity and inhibits oxidative phosphorylation in a tissue-autonomous manner, possibly by sequestering WNT3a. These results implicate local WNT signaling as an attractive target for combating obesity.

WNTs are secreted proteins that play important roles in the regulation of many different cellular functions, including growth and development. WNTs signal via frizzled receptors to activate intracellular signaling pathways that lead to the stabilization of β-catenin (the so-called canonical pathway), or they stimulate various β-catenin–independent signals, like Ca^{2+} influx or JNK activation (the noncanonical pathway) (1). Secreted frizzled-related proteins (SFRPs) containing cysteine-rich domains related to those of frizzled receptors negatively regulate WNT signaling by neutralizing WNTs extracellularly (2).

WNT signaling has previously been reported to play an important role in adipocyte differentiation. The activation of β-catenin by WNTs, including WNT6, WNT10a, and WNT10b, blocks adipocyte differentiation (3, 4). In contrast, the effects of the putative noncanonical ligands WNT4 and WNT5a on adipocyte differentiation remain the subject of controversy. It has been shown that knockdown of WNT4 or WNT5a diminishes adipocyte differentiation of 3T3-L1 preadipocytes (5); however, suppressive actions of WNT5a treatment have also been reported (6).

In this issue of the *JCI*, Mori, MacDougald, and colleagues report an unexpected role of SFRP5 on the oxidative capacity of adipocytes in vivo and ex vivo (7). The authors confirmed previous findings that *Sfrp5* mRNA expression is restricted to adipocytes within white adipose tissue (8, 9) and showed that *Sfrp5* expression was induced during late stages of adipocyte differentiation. Furthermore, they found that *Sfrp5* mRNA expression was upregulated

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