Thalassemia: An Overview of 50 Years of Clinical Research

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• Thalassemia • Hemoglobin • Erythrocyte • Transfusion

The thalassemias are a group of disorders that are attributable to the defective production of hemoglobin (Hb). The mature Hb molecule is a tetramer composed of 2 α-globin and 2 β-globin polypeptides, which assemble, along with a heme prosthetic group, to form the complete molecule. In the α-thalassemias, sufficiently defective production of α-globin chains results in decreased red cell (erythrocyte) Hb content and free β-globin polypeptides, which can assemble to form a moderately unstable Hb known as HbH. This unstable Hb causes a mild to moderate hemolytic and hypochromic anemia.[1] In the β-thalassemias, impaired production of β-globin chains result in unpaired α-globin chains, which are unstable in erythroid precursors, where they precipitate and cause membrane injury and unfolded protein responses and thereby lead to toxicity and death of these cells. This in turn causes ineffective erythropoiesis and the numerous clinical features of the disease.[2,3]

In the last 5 decades, a significant set of discoveries has illuminated the pathophysiology and enhanced the prevention and treatment of the thalassemias. This article briefly reviews many of the important advances in thalassemia that have occurred in this period. The study of the thalassemia syndromes has greatly enhanced the development and application of molecular biology to biomedical research. Patients with the thalassemia syndromes have contributed enormously to understanding of the molecular basis of health and disease. However, the application of these new approaches to the treatment of these disorders has been slow, particularly in the developing world where the diseases are common, but there is definite progress. The articles in this issue emphasize how ever increasing knowledge of cellular and molecular biology is facilitating the development of more effective therapies for these patients.

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THE MOLECULAR PATHOPHYSIOLOGY OF THALASSEMIA

Although the first clinical descriptions of the thalassemia syndromes were published by Cooley, Rietti, Greppi, and Micheli in 1925,[4] it took many more years before the pathophysiology of these diseases began to be elucidated. The first clues came from research in the 1950s that used protein chemistry to assess various Hb variants. Based on the extensive studies by numerous groups in this era, Ingram and Stretton[5] suggested that there were 2 groups of thalassemias, α and β, which were caused by defects in the synthesis of α- and β-globin polypeptides, respectively. Several years later, Fessas[6] suggested that the cause of the β-thalassemia syndromes could be attributable to unbalanced globin chain synthesis, with the disease manifestations resulting from the presence of intraerythroblastic inclusions of unpaired α-globin molecules. His prescient idea was confirmed by spectrographic observations with Thorell that the inclusions were indeed comprised largely of α-globin chains.[7] Several other workers, including Clegg, Weatherall, Marks, Weissman, and Nathan, came to similar conclusions about the pathophysiology of this disease and provided a great deal of experimental support for this hypothesis.[8–11]

However, with only the tools of protein chemistry available, the exact molecular basis of these diseases remained an enigma and a great deal of speculation took place in the era following these observations.[12–14] After much experimental work, an era of RNA analysis ushered in important new approaches to this problem and several seminal experimental observations followed. In the early 1970s, Benz, Forget, Kan, Nathan, Lodish, Marks, Bank, and Nienhuis showed that β-globin mRNA translation was reduced in patients with β-thalassemia, suggesting that this defect was caused by impaired or defective production of a functional mRNA.[15–18] With the discovery and isolation of reverse transcriptase, newer approaches to this problem became available because cDNA could be synthesized, and this rapidly led to the elucidation by Housman, Benz, Forget, Bank, and numerous others that the thalassemias appeared to be generally attributable to decreased globin mRNA levels.[19,20] Kan, Weatherall, and their colleagues, used α-globin cDNA probes to identify the first genetic mutations in thalassemia by showing that the α-globin genes were deleted in certain forms of α-thalassemia.[21,22]

Soon afterward, a highly productive period began with the identification of various thalassemia mutations and deletions. Numerous clinical scientists, including Kan, Forget, Weatherall, Orkin, Higgs, Kazazian, were empowered by the tools and insight provided by basic scientists such as David Baltimore, Phil Sharp, Tom Maniatis, Phil Leder, Harvey Lodish, and Daniel Nathans. The work began with the use of Southern blotting to elucidate deletions resulting in thalassemia. Although this was highly successful in the α-thalassemias,[23,24] it was of limited use in β-thalassemia, and only in specific instances.[25] This problem was solved with the use of gene cloning and DNA sequencing to identify point mutations that result in the thalassemias. In most instances, recurrent common mutations were found in many patients, making routine sequencing laborious and limited in its ability to identify new mutations. However, the finding that different β-globin gene mutations exist on haplotype blocks, at least at the β-globin locus, at first by Kan in sickle cell anemia and then by Antonarakis, Kazazian, and Orkin in β-thalassemia, helped to surmount this limitation.[26–28] This resulted in the discovery of hundreds of mutations that cause the thalassemia syndromes. Not only was a large set of mutations identified that result in the thalassemias, but this also led to the elucidation of many mechanisms that can impair mRNA production or function in the cell. Insights were gained into processes as diverse as transcription, mRNA modification, splicing, and translation.[1,4] These findings