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Review

Molecular basis of α-thalassemia

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A B S T R A C T

α-Thalassemia is an inherited, autosomal recessive, disorder characterized by a microcytic hypochromic anemia. It is one of the most common monogenic gene disorders in the world population. The clinical severity varies from almost asymptomatic, to mild microcytic hypochromic, and to a lethal hemolytic condition, called Hb Bart's Hydrops Foetalis Syndrome. The molecular basis are usually deletions and less frequently, point mutations affecting the expression of one or more of the duplicated α-genes. The clinical variation and increase in disease severity is directly related to the decreased expression of one, two, three or four copies of the α-globin genes. Deletions and point mutations in the α-globin genes and their regulatory elements have been studied extensively in carriers and patients and these studies have given insight into the α-globin genes are regulated. By looking at naturally occurring deletions and point mutations, our knowledge of globin-gene regulation and expression will continue to increase and will lead to new targets of therapy.

1. Introduction

Human hemoglobin is a tetrameric protein consisting of two alpha-like and two beta-like globin chains each forming a pocket containing the heme group for binding oxygen (David Gell, this issue). The globin genes are arranged in two separate gene-clusters on different chromosomal loci in order of their expression during development (Fig. 1). Expression is regulated by complex interactions of transcription factors and regulatory elements (promoters and enhancers) to switch on and off genes in a stage specific and tissue specific manner.

Globin gene disorders (hemoglobinopathies) are characterized by either abnormal globin chain variants like sickle cell anemia or reduced globin chain synthesis in erythroid cells (thalassemia) during hematopoiesis [1]. The hemoglobinopathies are inherited as mostly autosomal recessive traits. The reduction or absence of α-globin chains result in an excess of unpaired beta (β)-like globin chains which form insoluble homotetramers leading to intracellular precipitation, ineffective erythropoiesis and acute hemolytic anemia typical for the severe forms of α-thalassemia [2,3].

Thalassemia patient studies have played a crucial role in the identification of numerous causative mutations in the globin genes, the upstream or downstream untranslated regions, and the regulatory elements controlling the expression of the α- and β-globin gene families and thus the hemoglobin switch. Cell lines and mouse models have enabled the identification of a diverse collection of cooperating transcription factors and other protein complexes involved in the regulation of expression of these genes [4–6]. In spite of many animal models described to date, investigation of naturally occurring deletions and point mutations in carriers and patients is still essential to gain insight into regulation of expression and disease mechanisms. In the present review we'll highlight aspects of the molecular basis of α-thalassemia that provide insight into how we may understand the mechanisms underlying α-thalassemia [7,8].

2. Disease names and diagnosis

Alpha-thalassemia is characterized by a deficit in the production of the α-globin chains of hemoglobin. Individuals who carry a mutation affecting α-globin genes on a single chromosome, associated with mild anemia are said to have 'silent' α-thalassemia (if one gene is involved) or α-thalassemia trait (when two genes are involved), while compound heterozygotes or homozygotes expressing moderate to severe haemolytic anemia are known as having HbH disease. The excess of β-like globin chains form non-functional β chain tetramers called HbH (β_4 tetramers) in adults and γ chain tetramers called Hb Bart's (γ_4 tetramers) in the foetal period. The most severe form of α-thalassemia is a condition with no expression of α-genes and is called the Hb Bart's Hydrops Foetalis Syndrome (Fig. 2).

A rare syndrome, referred to as α-thalassemia/mental retardation syndrome of chromosome 16 (ATR16), is associated with very large deletions in 16p13.3 removing the α-globin genes and many other genes in and around the α-globin gene cluster (ATR16 syndrome,

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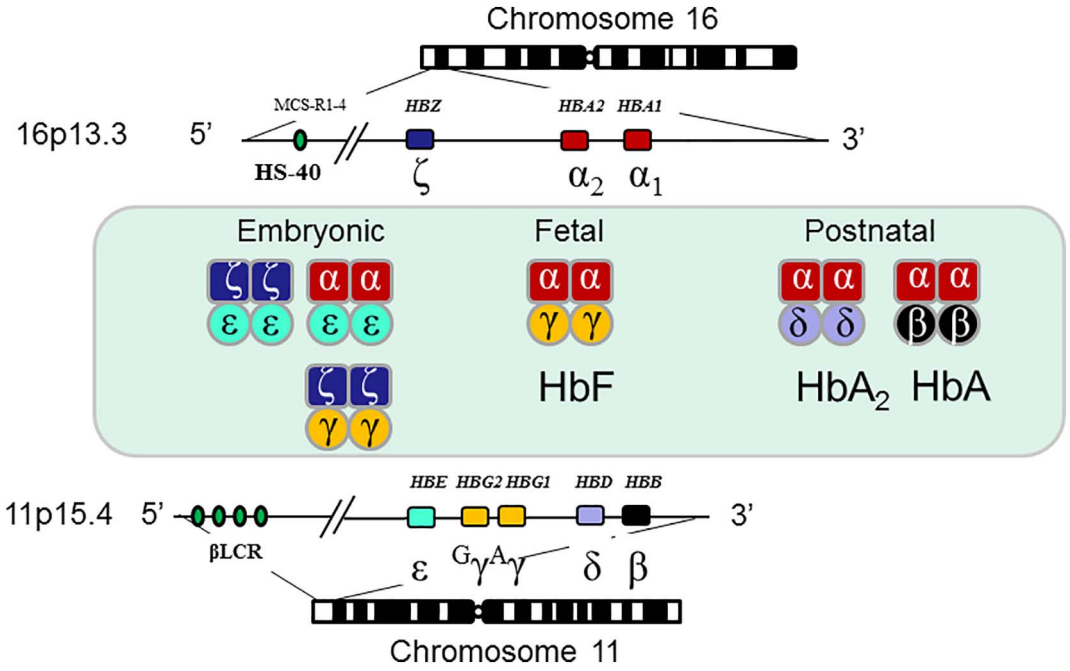

Fig. 1. Schematic presentation of the chromosomal location of the α- and β-globin gene clusters on 16p and 11p respectively. The embryonic and foetal genes are indicated as open boxes. The genes which remain active throughout postnatal life in grey and black. The different hemoglobins expressed during the embryonic period are shown, from left to right Hb Gower-1 (ζ2ε2), Hb Gower-2 (α2ε2) and Hb Portland (ζ2γ2), foetal period (HbF) and postnatal period (HbA and HbA_2).

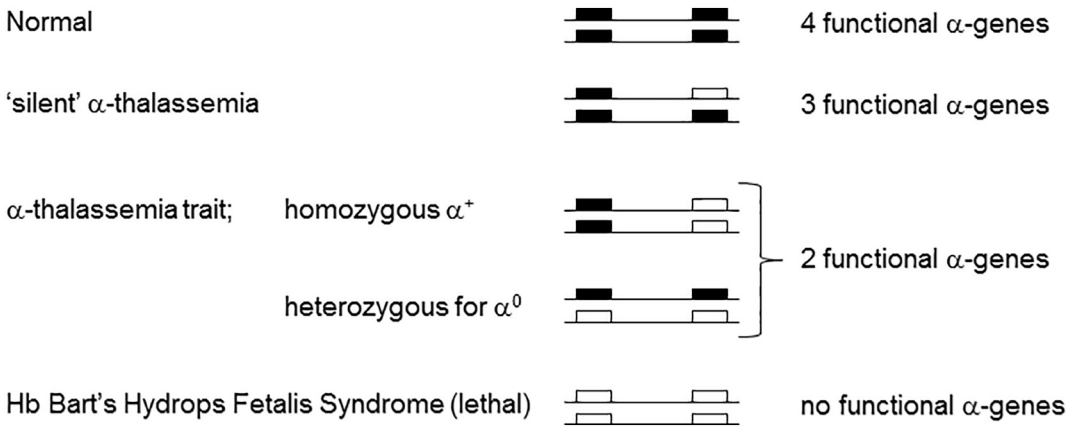

Fig. 2. Classification of α-thalassemia defects and phenotypic expression.

OMIM:141750) [9,10]. Besides marked microcytic hypochromic anemia, these patients present with a variable clinical phenotype characterized by mild to moderate intellectual disabilities, developmental delay and a wide range of less characteristic dysmorphic features. Patient analysis revealed that from the approximately 40 patients analysed to date, only 11 showed pure monosomy for the short arm of chromosome 16. The *SOX*-8 gene, strongly expressed in brain, was considered a strong candidate gene [11], however the description of a Brazilian HbH family showed none of the typical *ATR*-16 clinical features in spite of the loss of *SOX*-8 [12]. The outcome from these patient studies was that the clinical variation was so large that it could not be attributed to a single gene missing in the deleted area. One possibility is that the deletion of a large number of genes may unmask mutations normally compensated for by genes in its homolog. Another explanation could be that dosage sensitive genes may be present in the deleted area. In spite of the fact that only few *ATR*-16 patients could be investigated, imprinting doesn't seem to play a role as no major clinical differences have been seen between maternally and paternally derived chromosomes. The *ATR*-16 syndromes and the deletions involved have been extensively reviewed elsewhere [12–15].

Another rare syndrome associated with α-thalassemia is the X-linked mental retardation syndrome ATR-X. This syndrome is characterized by severe mental retardation and dysmorphic features showing striking similarities among patients. The mental retardation is more severe than in ATR-16 and involves some other clinical features such as severe psychomotor impairment, hypertelorism and facial dysmorphism like flat nasal bridge, triangular upturned nose, wide mouth and developmental abnormalities in genital and/or urogenital areas [16]. The molecular cause of ATR-X is mainly from point mutations in the *ATRX* gene (Xq13.3) encoding a chromatin-associated protein belonging to the SNF2 family of helicase/adenosine triphosphatases (ATRX OMIM:301040, reviewed elsewhere) [16].

Although the relationship between ATRX mutations and α-thalassemia is not completely clear, ATRX protein was found to be a transcriptional regulator affecting α-globin gene expression [17–19]. Furthermore, the presence in rbc's of HbH inclusion bodies, that contain insoluble β4 tetramers visible as inclusions after staining with 1% Brilliant Cresyl Blue, in some patients with ATRX syndrome implies the down-regulation of α-globin gene expression. On the other hand, not all patients present with HbH inclusions. As the ATP-dependent chromatin-