Krüppel-Like Factor 1 in Erythropoiesis

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Krüppel-like factor 1 (KLF1) is an erythroid-specific transcription factor that plays a crucial role in erythropoiesis. Isolated for the first time from mouse erythroleukemia cell line (MEL), it was originally named erythroid Krüppel-like factor (EKLF). When related Krüppel-like factors were subsequently identified, the nomenclature was changed to KLF1 to reflect the order of discovery. The human *KLF1* gene is located on chromosome 19p13.2, whilst the mouse *Klf1* gene is located on chromosome 8. KLF1 is a master erythroid gene regulator whose relevance in erythroid development and haemoglobin switching became clear as soon as the first *Klf1* KO mouse models were characterised. The process of erythropoiesis occurs in different organs during mammalian embryonic development. Primitive erythropoiesis occurs in the yolk sac, in which primitive erythroid precursors (i.e., erythroid-colony-forming cells, Ery-CFCs) arise and further differentiate in the bloodstream. Definitive erythropoiesis occurs in the foetal liver until birth and subsequently in the bone marrow. Definitive erythroblasts mature in specialised niches called erythroblastic islands, which are characterised by the central macrophages of erythroid islands (CMEIs) surrounded by maturing erythroblasts, which play a fundamental role in erythropoiesis homeostasis and nuclei digestion. Both Ery-CFC and definitive erythroid progenitors (BFU-E/CFU-E), undergo a further phase of differentiation, called terminal erythropoiesis starting from large nucleated cells, proerythroblasts, that differentiate to basophil, then polychromatic and, finally, orthochromatic erythroblasts.

KLF1 erythropoiesis haemoglobin switching human mutations

1. Regulation of Krüppel-Like Factor 1 (KLF1) Expression by Non-Coding RNA

The epigenetic regulation of KLF1 by non-coding RNA (ncRNA) has been investigated in the last few years. In particular, microRNAs (miRNAs or miRs), a class of small, non-coding linear RNA, represent an interesting field of investigation due to the relevance of this class of molecules as a therapeutic target [1]

MiR-326 has been identified as a direct inhibitor of KLF1 and positive correlation has been evidenced between its expression and foetal haemoglobin levels in reticulocytes from β-thalassemia major patients compared with healthy controls [2]. Moreover, altered KLF1 expression has been highlighted in K562 cells stably expressing MiR-34a [3] and the correlation between KLF1 levels and the up-regulation of miR-451 has been reported in murine embryonic stem cells [4]. The down-regulation of KLF1, BCL11A and MYB associated with up-regulation of miR-15a, miR-16, miR-26b and miR-151-3p has been described in K562 and differentiated erythroid human primary cells treated with hydroxyurea, suggesting a possible association between these miRNAs and the critical regulators of HbF expression [5].

Long non-coding RNAs (lncRNAs) are implicated in the regulation of KLF1 as well. Recently, a deep RNA-sequencing study identified a novel lncRNA (Gm15915), named lncEry, for its elevated expression in erythroid cells. lncEry seems to promote KLF1 expression, through interaction with WD repeat-containing protein 82 (WDR82) affecting early and late stages of erythropoiesis [6].

2. Human KLF1 Variants and Phenotypes

According to the Human Gene Mutation Database (https://www.hgmd.cf.ac.uk/ac/index.php, accessed on 31 May 2022), more than 130 KLF1 variants have been reported to date. These are classified into five classes corresponding to their effect on the gene: FP, functional polymorphism; DM, disease-causing mutation; DM? supposed disease-causing mutation; DP, disease-associated polymorphism; and DFP, disease-associated polymorphism with supporting functional evidence. The variants described to date have mostly been localised in the coding region, causing alterations in the primary structure of the protein. A smaller percentage (2.3%) are located in the *KLF1* promoter, affecting gene transcription. Mutations in the coding sequence can be further grouped into four subclasses according to their effect on protein function [7]: class 1 is represented by missense variants located outside the ZF domains, with no or minor functional effects; class 2 includes missense variants or small in-frame deletions that interfere with the normal function of KLF1, mostly located in the ZF domains; class 3 comprises stop codon or frameshift variants that result in truncated KLF1 proteins lacking the ZF domains; in class 4, a unique mutation (p.Glu325Lys) is localised in a highly conserved residue in ZF2, causing dominant severe congenital dyserythropoietic anaemia type IV [8][9]. KLF1 regulates approximately 700 genes in human erythroid cells, which are involved in a wide variety of molecular processes.

Many of them have previously been reported as murine KLF1 target genes [10]. These genes are sensitive not only to KLF1 expression levels (i.e., when one allele carries an inactivating mutation) but also to the type of *KLF1* mutation. Indeed, specific *KLF1* variants result in the altered expression of these genes, causing a wide range of benign and severe erythroid phenotypes. This emphasises the pleiotropic effect of KLF1 in wild-type and mutant conditions (**Table 1**). These phenotypes include the In(Lu) blood types, HPFH, increased levels of HbA_2 ($\alpha_2\delta_2$), congenital dyserythropoietic anaemia, hydrops foetalis, non-spherocytic haemolytic anaemia, red cell protoporphyrin, and pyruvate kinase deficiency (**Table 1**).

Table 1. Human KLF1 mutations. List of mutations, genotypes and phenotypes described in the present review. These data are sorted by location. Regulatory: the location of the mutation is relative to the transcriptional initiation site. WT: normal allele.

Mutation Type	Nucleotide Change	Predicted Amino Acid Change
Regulatory	-154C > T	
Regulatory	-124T > C	
Nonsense	c.89G > A	Trp30Term

Mutation Type	Nucleotide Change	Predicted Amino Acid Change
Nonsense	c.172C > T	Gln58Term
Nonsense	c.380T > A	Leu127Term
Missense	c.544T > C	Phe182Leu
Small insertion	c.526_527insCGGCGCC	Gly176AlafsX179
Small insertion	c.519_525dupCGGCGCC	Gly176ArgfsX179
Small deletion	c.569delC	Pro190LeufsX47
Nonsense	c.809C > A	Ser270Term
Nonsense	c.862A > T	Lys288Term
Nonsense	c.874A > T	Lys292Term
Missense	c.892G > C	Ala298Pro
Missense	c.895C > T	His299Tyr
Small insertion	c.954dupG	Arg319GlufsX34
Missense	c.902G > A	Arg301His
Missense	c.973G > A	Glu325Lys
Missense	c.983G > T	Arg328Leu
Missense	c.983G > A	Arg328His
Missense	c.991C > T	Arg331Gly
Missense	c.991C > T	Arg331Trp
Missense	c.994A > C	Lys332Gln
Missense	c.1003G > A	Gly335Arg
Missense	c.1012C > T	Pro338Ser
Missense	c.1012C > A	Pro338Thr
Monoallelic mutations genotypes-phenotypes		
Genotypes	**Phenotypes**	**References**
Lys292Term/WT	Blood group variant In(Lu)	[11]

Mutation Type	Nucleotide Change	Predicted Amino Acid Change
Arg319GlufsX34/WT	Blood group variant In(Lu)	[11]
Pro190LeufsX47/WT	Blood group variant In(Lu)	[11]
His299Tyr/WT	Blood group variant In(Lu)	[11]
Arg328Leu/WT	Blood group variant In(Lu)	[11]
Arg328His/WT	Blood group variant In(Lu)	[11]
Arg331Gly/WT	Blood group variant In(Lu)	[11]
Leu127Term/WT	Blood group variant In(Lu)	[11]
-124T>C/WT	Blood group variant In(Lu)	[11]
Lys288Ter/WT	HPFH	[12]
Ser270Term/WT	Increased HbA2 levels	[13]
Glu325Lys/WT	Type IV CDA	[8]
Compound heterozygous mutations genotypes-phenotypes		
Genotypes	**Phenotypes**	**References**
p.S270X/p.K332Q	HPFH and red cell protoporphyrin	[14]
Trp30Term/Arg319GlufsX34	Hydrops fetalis	[15]
Ala298Pro/Gly176AlafsX179	NSHA	[16]
Pro338Ser/Gly176ArgfsX179	NSHA	[17]
Pro338Thr/Gly176ArgfsX179	NSHA	[18]
Gly335Arg/Gly176ArgfsX179	NSHA	[19]
Arg331Trp/Gly335Arg	NSHA	[20]
Arg301His/Gly176ArgfsX179	NSHA	[19]
-154 C > T/Ala298Pro	NSHA	[20]
Gln58Ter/Ala298Pro	NSHA	[20]
Ala298Pro/Gly176ArgfsX179	NSHA and pyruvate kinase deficiency	[20]
Homozygous mutation genotype-phenotype		

tein basal cell adhesion molecule (BCAM). Since the expression of BCAM is highly sensitive to the level of functional *KLF1*, its variants cause a marked down-regulation of the *BCAM* gene generating the In(Lu) (inhibitor of Lutheran blood group) phenotype, as demonstrated by a transcriptomic analysis of erythroblasts from In(Lu) type donors when compared to a control group [11]. Further evidence of the impact of human *KLF1* variants on the Lutheran (LU)

Mutation Type	Nucleotide Change	Predicted Amino Acid Change
Genotype	Phenotype	References
Phe182Leu/Phe182Leu [11]	Increased HbA2 levels	[21]

KLF1 DNA ZF domains. One of these (Arg319GlufsX34) is predicted to cause a frameshift and another (Lys292Term) encodes a premature termination codon, whilst all others result in single amino acid substitutions (His299Tyr, Arg328Leu, Arg328His and Arg331Gly). The three mutations outside of the ZF domains result in a premature termination codon (Leu127Term), a frameshift (Pro190LeufsX47) and an altered GATA1 binding site in the *EKLF* promoter (-124T>C) [11]. Since the discovery of the effect of KLF1 on blood-group phenotypes, genotyping of the *KLF1* variant has become the focus of In(Lu) phenotype research. Unfortunately, very few population-based studies have been performed in this field [22][23][24], despite being particularly important in the transfusion management of difficult transfusion-related cases. *KLF1* variants are also associated with the reduced expression of other red cell membrane proteins that carry blood group antigens, such as the Indian (IN), P1PK, Landsteiner–Wiener (LW), Knops (KN), OK, RAPH and I blood group systems; however, most are less sensitive to its levels [11][22][25][26][27][28][29][30][31].

2.2. Globin-Expression Dysregulation

KLF1 transcription factor regulates the β-globin gene expression by binding to the CACCC box of the β-globin promoter [32]. A variant in this region (-87 mutation) causes β^+-thalassemia with elevated HbF levels [33][34]. *KLF1* is a master erythroid gene activator, as demonstrated by the fact that the -198 mutation localised in the γ-promoter creates a new binding site for *KLF1* that causes the British hereditary persistence of the HbF (HPFH) phenotype [35]. HPFH was also associated to the haploinsufficiency of KLF1, which was described for the first time in a Maltese family with HPFH (HbF levels: 3.3–19.5%) and caused by a nonsense (Lys288Term) mutation on a *KLF1* allele (**Table 1**). In the same family, functional studies revealed low levels of BCL11A, implying that the main cause of HPFH is an impaired expression of BCL11A, which is sensitive to KLF1 dosage [12]. However, subsequent data from a Sardinian family with HPFH caused by compound heterozygosity for two *KLF1* mutations did not support the haploinsufficiency of KLF1 as a cause of HPFH [14]. *KLF1* gene sequencing performed on two brothers of this family, with a marked increase in HbF (22.1–30.9%), revealed a genetic compound condition for a nonsense mutation (Ser270Term) inherited from the father and a missense mutation (Lys332Gln), inherited from the mother. The Ser270Term nonsense mutation is predicted to completely ablate the ZF domain and the ability of KLF1 to interact with DNA. The missense Lys332Gln mutation lies in the second KLF1 ZF domain and combination with the Ser270Term nonsense mutation further reduces KLF1 function (**Table 1**). In this family only individuals with two in trans *KLF1* mutations have HPFH, while the monoallelic loss of *KLF1* expression is associated with normal HbF levels. Furthermore, in this family, very high levels of zinc protoporphyrin associated with *KLF1* mutations were reported [14].

Finally, *KLF1* variants are associated with moderately increased levels of HbA2 (**Table 1**). The role of *KLF1* variations leading to a borderline HbA2 phenotype was first reported in the Sardinian population [13]. Overall, 52 of 145 subjects (35.9%) with borderline HbA2 were heterozygotes for *KLF1* mutations. Among these, the nonsense Ser270Term was the most frequent (80.8%), being found in 42 individuals. The mean HbA2 levels in these patients

were 3.6% ± 0.2 (reference value: 2.8% ± 0.2), with normal MCV and MCH [13]. Another study involving 65 borderline HbA2 cases (HbA2: 3.3–3.9%) revealed that 7.6% of these carried *KLF1* variations. The mean HbA2 level of these cases was found to be 3.52% ± 0.14. One patient homozygous for Phe182Leu variation with HbA2 of 3.4%, and HbF of 2.5%, was also found [21]. The molecular mechanism for borderline HbA2 is most likely explained by an increased LCR interaction with the competing *HBD* gene when compared to the *HBB* gene under diminished KLF1 expression, which increases the δ-globin gene expression with a consequent increase in HbA2 level [21].

2.3. Congenital Dyserythropoietic Anaemia (CDA)

CDA is a rare inherited red blood cell disorder with hallmarks of morphologic abnormalities of erythroblasts in the bone marrow and ineffective erythropoiesis and haemolysis, which can be divided into four subtypes (I–IV) based on erythroblast nuclear morphology [36]. The molecular aetiology of most CDA subtypes has been solved: type I is caused by mutations in codanin-1 (CDN1); type II is caused by mutations in SEC23B; type III is caused by mutations in KIF23 [37][38][39]. Rare type IV CDA cases are caused by a dominant mutation in *KLF1* (**Table 1**) [8][9][40][41]. The mutation consists of a G-to-A transition in one allele of *KLF1* exon 3, a change that results in the substitution of glutamic acid 325 by a lysine (p.Glu325Lys) in ZF2, which is highly conserved across KLF proteins from different species and across the entire KLF family. The p.Glu325Lys mutation leads to the abolition of the expression of the water channel AQP1 and the adhesion molecule CD44, and a reduced expression of two other adhesion molecules (BCAM and ICAM4). The peripheral blood contains evidence of poikilocytosis, anisocytosis, fragmented erythrocytes and many nucleated red blood cells. These nucleated red blood cells are mostly orthochromatic erythroblasts, which suggests a failure of terminal erythroid differentiation. Additionally, CDA IV is characterised by the very high expression of HbF (~35% of total Hb) and persistent expression of embryonic globin (HB-Portland) [8]. Notably, a variant in the homologous residue in mouse *Klf1*, Glu339Asp, underlies semi-dominant neonatal anaemia (Nan) [42][43]. Phenotypically, Nan mice display many similarities with CDA IV patients, and a limited subset of Klf1target genes is down-regulated in Nan mice [42][44][45], which may be helpful for the analysis of CDA IV patients. The E325K mutation reveals an altered DNA-binding specificity, both at canonical target sites (i.e., β-globin promoter) and aberrant binding to new sites causing ectopic transcriptional activation of non-erythroid genes. Based on in vivo and in vitro experiments, it is likely that CDA IV is caused by a general dysregulation of gene expression in developing erythroblasts that interferes with differentiation causing haemolysis. The E325K allele is probably hypomorphic to some known KLF1 target genes, such as CD44 and ICAM4, and neomorphic to other nonerythroid genes [45][46][47][48].

2.4. Hydrops Foetalis

The first case of a KLF1-null human was described in a patient with hydrops foetalis caused by compound heterozygosity for the Trp30Term and Arg319GlufsX34 null alleles (**Table 1**) [15]. The proband was born with severe non-spherocytic haemolytic anaemia (NSHA), hepatosplenomegaly and jaundice, which was difficult to control. There was marked erythroblastosis with erythroid expansion within the bone marrow and marked (76%) HPFH. The proband underwent a successful unrelated allogeneic bone marrow transplantation at 6 years of age but developed cerebral palsy due to kernicterus [15]. RNA-Seq was performed on peripheral circulating blood cells of

the proband and his parents and compared with published RNA-Seq datasets. Notably, 819 erythroid genes were poorly expressed when compared to normal definitive erythroblasts. Many of these have been previously reported as murine Klf1 target genes [10][25][30][49]. These encode for cytoskeletal proteins, heme synthesis enzymes, cell-cycle regulators, blood-group antigens and the chaperone AHSP (alpha-haemoglobin-stabilising protein). AHSP prevents the aggregation of α-globins during haemoglobin assembly [50]. It is a direct target gene of KLF1 and loss of expression in KLF1 mutant cells worsens the damage conferred by excess α-globin chains in β-thalassemia [51][52][53].

Moreover, the pattern of altered gene expression in erythroid cells was very similar to that reported for *Klf1*-null mice [15][25][26]. It is unclear whether the persistence of HbF explained birth survival or whether this infant had complementary variants that ameliorated the effects of KLF1 deficiency. Another report confirmed that in humans, although compatible with life, the loss of KLF1 severely impairs erythropoiesis [54].

2.5. Non-Spherocytic Haemolytic Anaemia (NSHA)

NSHA is a term for hereditary anaemias characterised by the reduced survival of red blood cells with abnormal morphology, erythroid hyperplasia in the marrow, and haemolysis. The term is usually applied once thalassemia, hereditary spherocytosis, enzymopathies and CDA have been excluded by molecular, enzymatic and morphological tests. The patients described to date have had transfusion-dependent haemolytic anaemia originally misdiagnosed as thalassaemia and are compound heterozygous for *KLF1* variants: Ala298Pro/Gly176AlafsX179 [16], Pro338Ser/Gly176ArgfsX179 [17], Pro338Thr/Gly176ArgfsX179 [18], Gly335Arg/Gly176ArgfsX179 [19], Arg331Trp/Gly335Arg, Arg301His/Gly176ArgfsX179, -154 C>T/Ala298Pro, Gln58Ter/Ala298Pro, Ala298Pro/Gly176ArgfsX179 [20]. Patients who are compound heterozygous for the latter two mutations also showed reduced levels of pyruvate kinase enzyme activity [20].

2.6. Red Cell Protoporphyrin

A family of Sardinian origin has been reported showing very high levels of zinc protoporphyrin in red blood cells (detected value of 306 µg/dL; reference value < 35 µg/dL). This phenotype was associated, as for HPFH, with compound heterozygous mutations of *KLF1* (**Table 1**) [14]. In patients with *KLF1* variants, iron levels are normal but iron is not efficiently incorporated into heme. In this situation, zinc may be incorporated into the heme instead of iron.

KLF1 coordinates expression of many of the genes involved in iron metabolism of erythroid precursors, including heme synthesis enzymes (e.g., ALAS2, ALAD, HMBS) [10][26][55][56] and proteins regulating the processing of iron (e.g., TFR2, SLC25A37, STEAP3, ABCG2, and ABCB10) [15][57]. KLF1 role in iron metabolism was demonstrated in a Nan mutant mouse that manifested a dramatic increase in the zinc protoporphyrin. This mouse model carried the Glu339Asp missense mutation, localised in the central Zn finger, which alters the DNA binding domain. The failure of *KLF1*-deficient cells to accumulate haemoglobin could be partly due to reduced heme synthesis since both processes are tightly linked [48][58].

2.7. Pyruvate Kinase Deficiency

Mutations in the *KLF1* gene in Thai paediatric patients have been described to cause the severe down-regulation (50% of normal) of pyruvate kinase (PK) levels, resulting in NSHA [20]. The PK enzyme is encoded by the *PKLR* gene and, once causative mutations in the coding region of *PKLR* were excluded by DNA sequencing, the *KLF1* gene was analysed, since it binds the *PKLR* gene promoter [59].

Patients' PK levels were pathologically reduced and abnormal red blood cells resembling the typical punctiform cells of PK deficiency were observed.

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