Krüppel-like factors: Three fingers in control

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Abstract
Krüppel-like factors (KLFs), members of the zinc-finger family of transcription factors capable of binding GC-rich sequences, have emerged as critical regulators of important functions all over the body. They are characterised by a highly conserved C-terminal DNA-binding motif containing three C2H2 zinc-finger domains, with variable N-terminal regulatory domains. Currently, there are 17 KLFs annotated in the human genome. In spite of their structural similarity to one another, the genes encoding different KLFs are scattered all over the genome. By virtue of their ability to activate and/or repress the expression of a large number of genes, KLFs regulate a diverse array of developmental events and cellular processes, such as erythropoiesis, cardiac remodelling, adipogenesis, maintenance of stem cells, epithelial barrier formation, control of cell proliferation and neoplasia, flow-mediated endothelial gene expression, skeletal and smooth muscle development, gluconeogenesis, monocyte activation, intestinal and conjunctival goblet cell development, retinal neuronal regeneration and neonatal lung development. Characteristic features, nomenclature, evolution and functional diversities of the human KLFs are reviewed here.

Keywords: gene expression, zinc-finger, transcription factor, Krüppel-like factor, DNA-binding

Introduction
Krüppel-like factors (KLFs) are members of the zinc-finger family of transcription factors named after their similarity to the Drosophila gap gene Krüppel.1 KLFs are characterised by a DNA-binding motif containing three well-conserved C2H2 zinc-finger domains located in the carboxy terminal of the protein capable of binding GC-rich sequences, such as CACCC elements present in the proximal promoters of many eukaryotic genes.2–7 The transcriptional regulatory domains located in the amino terminal of different KLFs are variable, resulting in their ability to interact with co-activators and/or co-repressors, culminating in the activation or repression of a given promoter activity. The presence of variable structural motifs outside of the DNA-binding domain of the KLF family members is reflected in their functional diversity.3,8 Characteristic features, nomenclature, evolution and functions of the human KLFs are reviewed here.

Characteristic features of the zinc-finger domain in KLFs
The 81-amino acid DNA-binding zinc-finger domain is highly conserved among the members of the KLF family, with more than 65 per cent amino acid sequence identity among the family members. The specific amino acids critical for DNA binding are highly conserved, imparting an ability to different KLFs that interact with similar â€œ-elements,
such as GT boxes or GC-rich sequences like CACCC. The C$_2$H$_2$ zinc finger present in the KLFs consists of two short beta strands followed by an alpha helix. In the classical C$_2$H$_2$ zinc-finger domain, two conserved cysteines and histidines coordinate a zinc ion. The pattern of amino acid arrangement in a classical zinc finger is as follows: #-X-C-X(1-5)-C-X3-#-X2-H-X(3-6)-[H/C], where C, H and X correspond to cysteine, histidine and any amino acid, respectively, and numbers indicate the number of residues separating the flanking amino acids. The amino acids that are important for the stable fold of the zinc finger are marked with the # symbol. The amino acid occupying the final position can be either histidine or cysteine. The linker sequence in between the

| Gene symbol | Gene name                  | Gene location       | Number of exons | Sequence IDs         | Previous symbols/aliases |
|-------------|----------------------------|---------------------|-----------------|----------------------|--------------------------|
| KLF1        | Krüppel-like factor 1      | 19p13.13–p13.12     | 3               | U37106 NM_006563     | EKLF                     |
| KLF2        | Krüppel-like factor 2      | 19p13.13–p13.11     | 3               | AF123344             | LKLF                     |
| KLF3        | Krüppel-like factor 3      | 4p14                | 6               | AF285837             | BKLF                     |
| KLF4        | Krüppel-like factor 4      | 9q31                | 5               | AF022184 NM_004235   | EZF, GKLFL               |
| KLF5        | Krüppel-like factor 5      | 13q22.1             | 4               | D14520               | BTEB2, IKLF, CKLF         |
| KLF6        | Krüppel-like factor 6      | 10p15               | 4               | U51869               | BCD1, ST12, COPEB, CPBP, GBF, Zf9, PAC1 |
| KLF7        | Krüppel-like factor 7      | 2q32                | 4               | AB015132 NM_003709   | UKLF                     |
| KLF8        | Krüppel-like factor 8      | Xp11.21             | 6               | U28282 NM_007250     | BKLFL3, ZNF741, DXS741   |
| KLF9        | Krüppel-like factor 9      | 9q13                | 2               | BC069431 NM_001206   | BTEB1                    |
| KLF10       | Krüppel-like factor 10     | 8q22.2              | 4               | U21847               | TIEG, EGRA, TIEG1        |
| KLF11       | Krüppel-like factor 11     | 2p25                | 4               | AF028008 NM_003597   | TIEG2, TIEG3             |
| KLF12       | Krüppel-like factor 12     | 13q22               | 8               | AJ243274 NM_007249   | AP–2rep, HSPC122, AP2REP |
| KLF13       | Krüppel-like factor 13     | 15q12               | 2               | AF132599 NM_015995   | RFLAT–1, BTEB3, NSLP1, FKLF–2 |
| KLF14       | Krüppel-like factor 14     | 7q32.3              | 1               | AF490374 NM_138693   | BTEB5                    |
| KLF15       | Krüppel-like factor 15     | 3q13–q21            | 3               | AB029254 NM_014079   | KKLFL                    |
| KLF16       | Krüppel-like factor 16     | 19p13.3             | 2               | AF327440             | NSLPG2, BTEB4, DRRF      |
| KLF17       | Krüppel-like factor 17     | 1p34.1              | 4               | BC049844 NM_173484   | ZNF393, Zfp393, FLJ40160 |
zinc-finger domains (TGE(R/K)P(Y/F)X) is also highly conserved in KLF proteins.9

**Nomenclature of KLFs**

The nomenclature of KLFs has evolved over the years. KLFs were initially named after the tissue in which they were detected or highly expressed, such as erythroid KLF (EKLF or KLF1),10 lung KLF (LKLF or KLF2),11 gut–enriched KLF (GKLF or KLF4),12–15 and intestinal–enriched KLF (IKLF or KLF5; also called BTEB2).16,17 A few other KLFs were named after the elements they bound, such as the core promoter–binding protein (CPBP/Zf9 or KLF6),18,19 basic transcription element-binding protein (BTEB1 or KLF9)20 or by their physiological responses, such as transforming growth factor–β-inducible early genes 1 and 2 (TIEG1 and TIEG2 or KLF10 and KLF11, respectively).21,22 Considering that the tissue expression of KLFs, the range of their nucleotide recognition sequences and their ability to regulate diverse functions is much broader than initially understood, the use of numerical nomenclature based on the chronological order of discovery (such as KLF1, KLF2, KLF3...) is recommended by the Human Genome Organization Gene Nomenclature Committee (HGNC) to avoid misleading connotations providing partial descriptions of their expression and/or function. A search of the HGNC website (http://www.genenames.org/index.html) for ‘Krüppel-like factor’ on 26th January 2010 identified 17 KLF genes in the human genome. Names, chromosomal locations, sequence accession IDs, previous symbols and aliases, if any, for these KLFs are given in Table 1. Several other related proteins, such as the members of the Sp family of proteins, GLI2, GLI3, and the pseudogene KLF7P, are not included in this list, for the sake of brevity.

**Evolution of KLFs**

KLFs are closely related to the Sp family of zinc-finger transcription factors, of which there are nine members in the human genome (Sp1–Sp9). Currently, there are 17 KLFs annotated in the human genome. The high level of conservation of structure and function of KLF proteins in different species is a reflection of their ancient evolutionary history. The 17 genes encoding different KLFs are scattered all over the human genome, and there are also 17 Klf genes in the mouse genome. This indicates that these genes are ancient and suggest the involvement of gene duplications and translocations in their evolution.

The exon–intron organisation of human KLF genes is not well conserved. For example, while KLF12 has eight exons, KLF14 is encoded on a single exon (Table 1). Based on an extensive phylogenetic analysis with the amino acid sequences of KLF proteins from different species, it was proposed that the mammalian KLF genes have evolved in two phases – the first in the chordate...
Table 2. Expression pattern, interacting co-factors, effect on gene expression and known functions of different KLFs.

| Gene | Expression pattern | Interacting co-factors | Cellular function | References |
|------|--------------------|------------------------|-------------------|------------|
| KLF1 | Erythroid and mast cells | P300/CBP, PCAF, SWI/SNF and mSin3A | Erythropoiesis, cell cycle | 25,26 |
| KLF2 | Lung, blood vessels, lymphocytes | WWP1 | Adipogenesis, lung and blood vessel development, T-cell migration, monocyte activation | 27,28–30 |
| KLF3 | Adipocytes, brain and erythroid tissue | CtBP2, FHL3 | Adipogenesis | 31,32 |
| KLF4 | Gut, skin, cornea and several other epithelial tissues | HDAC, p300/CBP, b−catenin/TCF4, Oct4, Sox2, CtBP | Epithelial barrier formation, goblet cell development, adipogenesis, stem cell maintenance, control of cell proliferation, regulation of neuronal regeneration | 33–39 |
| KLF5 | Gut, skin, lung, cornea and several other epithelial tissues | P53, HDAC1, PARP1, PIAS1 | Cell growth, lung development, cardiac remodelling, stem cell maintenance | 40–45 |
| KLF6 | Ubiquitous | HDAC3 | Tumour suppressor | 46 |
| KLF7 | Ubiquitous | MoKA | Cell proliferation, neuronal differentiation, olfactory bulb development | 47–51 |
| KLF8 | Ubiquitous | CtBP2 | Cell proliferation, epithelial to mesenchymal transition | 52–55 |
| KLF9 | Ubiquitous | mSin3A | Neurite outgrowth, carcinogen metabolism, intestinal epithelial development | 56–58 |
| KLF10 | Ubiquitous | mSin3A | Apoptosis, cell proliferation | 22, 59 |
| KLF11 | Ubiquitous | mSin3A, p300 | Cell proliferation | 60,61 |
| KLF12 | Brain, kidney, liver and lung | CtBP1 | Cancer progression | 62,63 |
| KLF13 | Ubiquitous | mSin3A, p300, PCAF | Cell proliferation, carcinogen metabolism | 64,65 |
| KLF14 | Ubiquitous | mSin3A, HDAC2 | Lipoprotein metabolism, basal cell carcinoma, TGF-β signalling | 66–68 |
| KLF15 | Ubiquitous | Sp1, MEF2A | Cardiomyocyte hypertrophy, gluconeogenesis | 69–71 |
| KLF16 | Ubiquitous | mSin3A | Carcinogen metabolism, cell cycle | 65,72 |
| KLF17 | Testis, brain and bone | Not known | Epithelial–mesenchyme transition | 73,74 |

Key
TGF-β, transforming growth factor-beta.
lineage, during the early emergence of vertebrates, and the second in the mammalian lineage. This phylogenetic analysis also identified six different ascidian zinc-finger proteins as the ancestral genes for the distinct subgroups of vertebrate KLF genes. In view of the intron-less nature of KLF14 and its homology with KLF16, it has been suggested that KLF14 is an ancient retrotransposed copy of KLF16. Phylogenetic analysis of the 17 human KLF complete amino acid sequences by the neighbour-joining method using the ClustalW2 program (http://www.ebi.ac.uk/Tools/es/cgi-bin/clustalw2) indicated that KLFs 5, 17 and 8 are related more to each other than to the rest of the KLFs, which are further grouped into two major clades (Figure 1). According to this analysis, KLFs 9 and 16 are the most recent KLFs to have diverged from each other, followed by KLFs 6 and 7 (Figure 1). This is consistent with the similar expression pattern, common ability to interact with mSin3A (a core component of a large multiprotein co-repressor complex with associated histone deacetylase enzymatic activity) and shared cellular function of cell cycle regulation attributed to KLFs 9 and 16 (Table 2).

Functions of KLFs

By virtue of their ability to activate and/or repress the expression of a large number of genes, KLFs regulate a diverse array of developmental events and cellular processes such as haematopoiesis, cardiac remodelling, adipogenesis, maintenance of stem cells, epithelial barrier formation, control of cell proliferation and neoplasia, flow-mediated endothelial gene expression, skeletal and smooth muscle development, gluconeogenesis, monocyte activation, intestinal and conjunctival goblet cell development, ocular surface integrity, retinal neuronal regeneration and neonatal lung development (Table 2). This functional diversity of KLFs is consistent with the variable amino terminal regulatory domains in different KLFs that allow interaction with a diverse array of co-factors. For example, KLFs 3, 8 and 12 interact with carboxy-terminal binding protein (CtBP) co-repressors through the PVDL(S/T) repressor domain, while KLFs 9, 10, 11, 13 and 16 interact with histone deacetylases (HDACs) through a Sin3 interaction domain (SID), both resulting in transcriptional repression. KLF4 interacts with co-activators such as p300 and CBP (cyclic-AMP-response-element-binding-protein-binding-protein) to mediate transcriptional activation. KLF4 also has the ability to interact with HDACs, to repress transcription. The functional diversity of KLFs results in interesting conflicts, wherein different KLFs have antagonistic effect(s) on individual cellular processes. For example, KLF4 suppresses cell proliferation, while KLF5 promotes it. Similarly, adipogenesis is supported by KLFs 4, 5 and 15, but is suppressed by KLFs 2 and 3.

Future directions

A large body of work over the past 25 years has established the KLFs as critical regulators of diverse functions in many parts of the body. In spite of this progress in our understanding of the properties of KLFs, much remains to be uncovered. In order fully to understand the properties of KLFs in diverse spatio-temporal contexts and physiological conditions, it is crucial to identify (a) the co-factors that they interact with; (b) their target genes; (c) the signal transduction pathways by which they are regulated; and (d) their unique tissue-specific roles using conditional knockouts. It is expected that these avenues of research will lead to exciting discoveries regarding the involvement of KLFs in human health and disease.

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