Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section
Mini Review

MAFA (v-maf musculoaponeurotic fibrosarcoma oncogene homolog A (avian))

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Identity

Other names: RIPE3b1; KLRG1; Maf-A,: hMafA; L-Maf

HGNC (Hugo): MAFA

Location: 8q24.3

Local order: C8orf51, RHPN1, MAFA, ZC3H3, GSDMD

DNA/RNA

Note
The MAFA open reading frame is encoded by a unique exon. The entire genomic organization and the putative existence of non-coding exons remain unknown.

Transcription

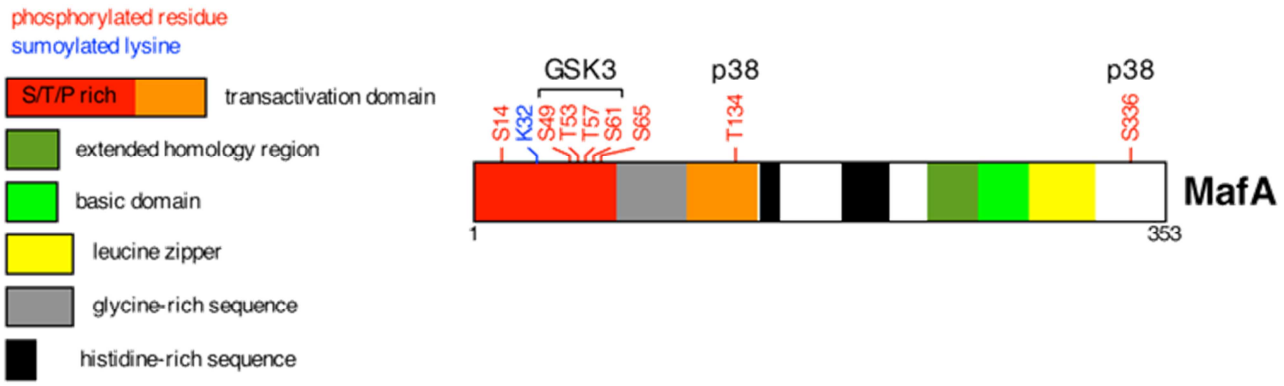
MAFA displays a restricted expression pattern. It is notably expressed in pancreas (in beta-cells) and lens.

Pseudogene

Unknown.

Protein

Note
Maf oncoproteins are b-ZIP transcription factors that belong to the AP-1 super-family, which notably includes JUN and FOS. The Maf family contains seven members, which can be subdivided into two groups; the large and small Maf proteins. While the small Maf proteins, MAFF, MAFG and MAFK, are essentially composed of a b-Zip domain, the large Maf proteins, MAFA/L-MAF, MAFB, MAF/c-MAF and NRL contain an additional amino-terminal transactivation domain. MAFA was initially cloned in quail and chicken species and named MAFA and L-MAF, respectively. More recently, mammalian MAFA was cloned and identi-fied as an essential component of the RIPE3b1 complex, which binds the insulin promoter.



Schematic representation of the MAFA protein structure. Critical residues involved in post-translational modifications are indicated by the color code. The kinases responsible for S14 and S65 phosphorylation in MAFA remain to be identified. GSK-3 phosphorylates the transactivation domain of MAFA, thereby inducing its ubiquitination and proteasome-dependent degradation. This is linked to an increase in MAFA transactivation. These phosphorylations are required for MAFA transforming activity. In contrast, sumoylation of MAFA transactivation domain decreases its transactivation activity.

Description

MAFA, like all large Maf proteins, contains an amino-terminal transactivation domain and a carboxy-terminal b-ZIP DNA binding domain. Large Maf proteins stimulate transcription of their target genes through their binding to two types of palindromic sequences called TRE- or CRE- type MARE (Maf Responsive Element) (TGCTGAC(G) TCAGCA). The leucine zipper domain allows the formation of homo- or hetero-dimers, an absolute pre-requisite for DNA binding. As homodimers, these proteins recognize palindromic sequences, with the basic domain contacting DNA directly. Among the AP-1 family, the Maf proteins are defined by the presence of an additional homolo-gous domain, called the Extended Homology Region (EHR) or ancillary domain, which also contacts DNA. Consequently, they recognize a longer palindromic sequence than other AP-1 family members. The MARE sequence is composed of a TRE or CRE core contacted by the basic domain and a TGC flanking sequence, which is recognized by the EHR domain. While the TGC motif is crucial for Maf binding, the TRE/CRE core can be more degenerate. MAFA transactivation activity and stability is regulated by post-trans-lational modifications (phosphorylation, ubiquityla-tion and sumoylation) mostly occuring on the transactivation domain. GSK-3 was identified as the major protein kinase regulating MAFA activity and oncogenic properties.

Expression

Endogenous MAFA protein is detected and phos-phorrylated in pancreatic beta cells.

Localisation

Nucleus.

Function

During development, Maf proteins are involved early in specification and later in terminal differen-tiation. MAFA is involved in the regulation of insulin gene expression in pancreatic beta cells. Accordingly, MAFA ablation in mice leads to diabetes.
Besides their roles during development, large Maf proteins, MAFA, MAFB, and MAF/c-MAF are also involved in oncogenesis.

Homology

MAFB and MAF/c-MAF are the closest MAFA homologs. The MAFA entire protein sequence shares 52%, 48% and 40% identity with those of MAFB, MAF/c-MAF and NRL, respectively. MAFA DNA binding domain (EHR + b-ZIP) shares 82%, 83%, 64% and 55-60% identity with those of MAFB, MAF/c-MAF, NRL and small MAFs, respectively. MAFA and JUN share 30% sequence identity in their b-ZIP domain (20% identity in their entire sequence).

Implicated in

Multiple myeloma

Hybrid/Mutated gene

Two cases reported translocations of MAFA to the immunoglobulin heavy-chain (IgH) locus, juxta-posing the MAFA gene with the strong enhancers of the IgH locus (meeting report, accurate description lacking).

Oncogenesis

Large Maf proteins, MAFA, MAFB, and MAF/c-MAF are bona fide oncogenes as demonstrated in tissue culture, animal models and in human cancers. MAFA displays the strongest transforming activity, in vitro. In human, MAF/c-MAF, MAFB and MAFA genes are translocated to the immunoglo-bulin heavy chain (IgH) locus in 8-10% of multiple myelomas. MAFA translocations are present in less than 1% of multiple myelomas. MAF/C-MAF over-expression plays a causative role in multiple myeloma by promoting proliferation and patholo-gical interactions with bone marrow stroma.
The transforming activity of Maf proteins is context dependent and they can occasionally display tumor suppressor-like activity in specific cellular settings. Their transforming activity relies on overexpression and does not require an activating mutation (no activating mutation has been identified to be associated with human cancers). It is regulated by post-translational modifications, notably phospho-rylation.

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