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Gene Section
Mini Review

ING2 (inhibitor of growth family, member 2)

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Identity

Other names: ING1L; ING1Lp; p32; p33ING2

HGNC (Hugo): ING2

Location: 4q35.1

DNA/RNA

Description

The two isoforms share exon 2 but have different exon 1. The exon 1a of ING2a encodes 58 amino acids. Exon 1b of ING2b encodes 18 amino acids. There is no significant homology between the N-terminal part of ING2b and the N-terminal regions of ING1 isoforms (Unoki et al., 2008).

Transcription

The promoter region of ING2a possesses two p53 binding sites in contrast to the promoter of ING2b. Binding of p53 to these sites suppresses the ING2a expression. The promoter region of ING2b harbors a HSF1 and HSF2 binding site, a c-Rel, a SP1 and five MZF1 binding sites (Unoki et al., 2008).

Protein

Description

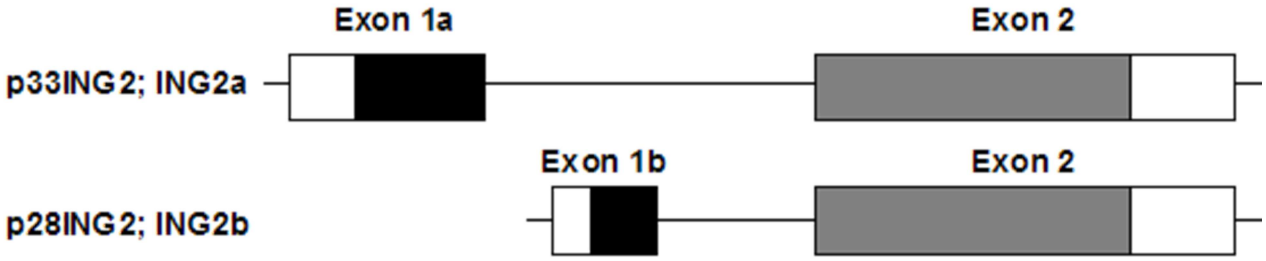
p33ING2a: 280 amino acids; 33kDa protein; harbor, listed from the N-terminal to the C-terminal region, a leucine-zipper-like-region (LZL), a novel conserved region (NCR), a nuclear localization signal (NLS), a plant homeo domain (PHD) finger motif and a poly basic region (PBR); p28ING2b: 240 aa; 28 kDa protein; lacks leucine-zipper-like-domain (LZL) is distinct to the N-termi-nal part to ING2a (Unoki et al., 2008).

Expression

ING2 is widely expressed in normal tissues (Shimada et al., 1998).

Localisation

ING2 is predominantly localized in the nucleus to chromatin and the nuclear matrix (Gozani et al., 2003). Through reduced levels of phosphoinositide PtdIns5P, ING2 might be released from chromatin and translocates partially to the cytoplasm (Gozani et al., 2003).



Gene structure of ING2a and ING2b (modified according to Unoki et al., 2008).

Function

The tumor suppressor protein ING2 has been described to regulate cell cycle, cellular senescence and gene regulation including chromatin level. In response to DNA damage ING2 enhances the acetylation of p53, which negatively regulates cell proliferation (Nagashima et al., 2001). In addition the level of ING2 expression directly regulates the onset of replicative senescence through the induc-tion of p300-dependent acetylation of p53 (Pedeux et al., 2005). ING2 also induces the global histone H4 acetylation and chromatin relaxation and thereby enhances the nucleotide excision repair (Wang et al., 2006). Furthermore, ING2 is also a part of two related mSin3/HDAC1/HDAC2 corep-ressor complexes (Doyon et al., 2006). Further, chromatin association of ING2 is linked to ING2 ability to bind to trimethylated K4 of histone 3 (H3K4me3) via its plant homeodomain (PHD) region (Shi et al., 2006). p33ING2 is also associated with histone methyltranferase (HMT-) activity in vitro and in vivo, methylating specifi-cally histone H3 and histone H1 (Goeman et al., 2008). In addition, ING2, as a transcriptional rep-ressor, directly interacts with the corepressor Alien and enhances the Alien-mediated gene silencing (Fegers et al., 2007). Furthermore, ING2 interacts with the Smad-interaction transcriptional modulator SnoN mediating TGF-beta-induced Smad-depen-dent transcription and cellular responses (Sarker et al., 2008). The activity of ING2, as a nuclear phosphatidylinositol receptor can be modulated by phosphoinositides (Gozani et al., 2003).

Homology

The PHD-finger motif is highly-conserved among all ING genes. There are five human ING genes (ING1, ING2, ING3, ING4, ING5) which encode multiple isoforms via splicing. So far known ING2 gene encodes two isoforms (ING2a: 33kDa; ING2b: 28kDA).

Mutations

Note

So far natural occurring point mutations of ING2 in association with cancer were not yet described. However, loss of heterozygosity (LOH) and aberrant ING2-mRNA levels were associated with cancer.

Implicated in

Colon cancer

Oncogenesis

ING2 expression level in human colon tumors is significantly higher than in normal colon tissue. In conclusion, ING2 might be involved in colon cancers (Shimada et al., 1998).

Hepatocellular carcinoma (HCC)

Oncogenesis

ING2 transcription and post-transcription level is downregulated in the majority of HCC tumors compared with non-tumors liver tissue. Further-rmore, ING2 expression level is reduced in 44 of 84 (52.4%) HCC cases and the ING2 expression level correlated with tumor size, histopathologic classifi-cation and serum AFP (Zhang et al., 2008). It is also shown that HCC patients with reduced ING2 expression have a significantly increased risk exhibiting a shorter survival time. In conclusion, ING2 may be involved in the progression of HCC (Zhang et al., 2008).

Head and neck squamous cell carcinoma (HNSCC)

Oncogenesis

There is a loss of heterozygosity (LOH) in the region 4q32 in the long arm of the chromosome 4 in 20% of the cases (Borkovsky et. al., 2008). This region includes ING2 and SAP30 genes that are parts of the two related mSin3/ HDAC1/2 corepres-sor complexes. LOH on region 4q35.1 was detected in 30 (54.6%) out of 55 informative cases (Borkovsky et. al., 2008). High LOH frequency is associated with advanced tumor stages; therefore, ING2 LOH is likely to be a late event in HNSCC.

Lung cancer

Oncogenesis

Although, there are no ING2 mutations identified in 30 human lung cancer cell lines and 31 primary lung cancer tumors. The ING2 mRNA expression is reduced in 6 out of 7 lung cancer cell lines (Okano et al., 2006).

Cutaneous melanomas

Oncogenesis

The nuclear expression level of ING2 is significantly reduced in human melanomas compared to dysplastic nevi. It is suggested that reduced ING2 expression may be involved in the initiation of melanoma (Lu et al., 2006; Ythier et al., 2008).

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