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Gene Section

Review

DIABLO (diablo, IAP-binding mitochondrial protein)

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Identity

Other names: DFNA64, DIABLO-S, SMAC, SMAC3

HGNC (Hugo): DIABLO

Location: 12q24.31

DNA/RNA

Description

The gene encompasses 19.86 kb of DNA; 7 exons.

Transcription

mRNA 2265 pb; ORF 720 pb.
Smac promoter contains a functional CRE site which is regulated by cAMP for apoptosis modulation (Martinez-Velazquez et al., 2007). Another transcriptional regulator for Smac is E2F1 which have two binding sites in the Smac promoter. Positive regulation of Smac by E2F1 results in enhanced mitochondria-mediated apoptosis (Xie et al., 2006).

Protein

Description

Precursor 239 aa (27.131 kDa), mature 184 aa (20.765 kDa).
- aa 1-55, mitonchondrial targeting sequence (MTS)
- aa 56-60 (AVPI) IAP-binding motif (IBM).
Post translational modifications:
- Ubiquitination, Hip2 (Bae, 2010), Livin (Ma, 2006), XIAP (Morizane, 2005; MacFarlane, 2002), cIAP1 (Hu and Yang, 2003), cIAP2 (Hu and Yang, 2003), Apollon (Hao et al., 2004).
- Phosphorylation, JNK3 (Park et al., 2007).

Expression

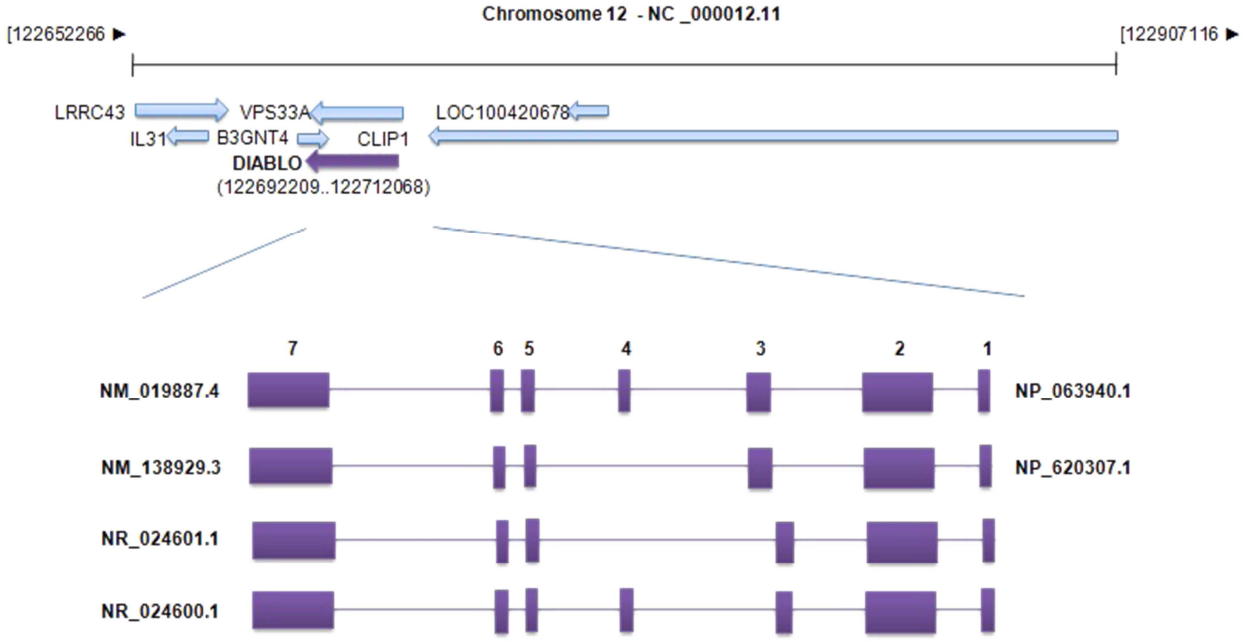
Ubiquitously, highest in adult testis and high in heart, liver, kidney, spleen, prostate and ovary. Smac mRNA is low in brain, lung, thymus and peripheral blood leukocytes (Du et al., 2000).

Localisation

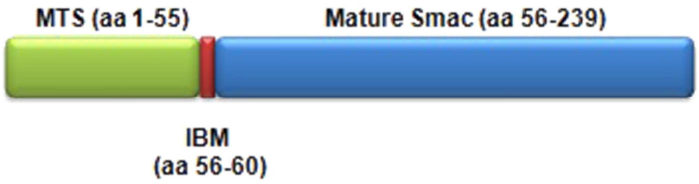
Mitochondrial (Du et al., 2000), cytosolic, after apoptosis activation (Du et al., 2000; Verhagen et al., 2000).

Function

Proapoptotic protein. Smac participates in both apoptotic pathways, intrinsic and extrinsic. Mature Smac localizes in mitochondria and after an apoptotic stimulus is released into the cytosol where it bind IAPs and neutralizes its inhibitory action on caspases (Du et al., 2000; Verhagen et al., 2000).
From the IAP family, Smac interacts with and inhibit XIAP (Du et al., 2000; Srinivasula et al., 2000), cIAP1 (Hu and Yang, 2003), cIAP2 (Hu and Yang, 2003), Survivin (Song et al., 2003; Kim et al., 2006), Apollon (Hao et al., 2004; Qiu and Goldberg, 2005) and ML-IAP/BIRC7 (Vucic, 2002). Recently, an apoptosis-independent role for Smac in colon cancer has been described. Loss of Smac induces cIAP1 and cIAP2 upregulation, increased proliferation and activation of the NF-kB p65 subunit (Qiu et al., 2012).



Structure of Smac gene and its transcripts.



Structure of Smac. Smac is a protein of 239 aa. MTS: mitochondrial targeting sequence; IBM: IAP-binding motif; aa: aminoacids.

Homology

The gene in conserved in chimpanzee, dog, cow, mouse, rat, chicken and zebrafish.

Mutations

Germinal

A heterozygous missense mutation, c.377C>T, in Smac, is genetically linked to progressive, non-syndromic, sensorineural hearing loss in an extended Chinese DFNA64 family.

Prediction by molecular modeling localizes this mutation at the end of the arch-shaped H1 helix, far away from the binding site to IAPs. Although the mutation does not alters the apoptotic function of Smac, ectopic expression of the mutant induces degradation of both, endogenous and mutant Smac through heterodimerization between them (Cheng et al., 2011).

Implicated in

Preeclampsia

Note

Significantly elevated levels of Smac were found in villous trophoblast in pregnancies complicated by preeclampsia in comparison with normal pregnancies. This upregulation may be related to increased apoptosis in preeclampsia (Heazell et al., 2008).

Hepatocellular carcinoma

Note

mRNA and protein expression of Smac was significantly different in tissues of hepatocellular carcinoma and non hepatocellular carcinoma tissues. Smac expression is diminished in carcinoma (Bao et al., 2006).

Pancreatic cancer

Note

Smac protein, by immunohistochemistry analysis, was significantly upregulated in pancreatic tumours. Smac expression was correlated only with pathological grade ($p<0.05$) (Hu et al., 2012).

Bladder cancer

Note

Smac expression is downregulated in bladder cancer, this reduced level predicts a worse prognosis (Mizutani et al., 2010).

Even, the mean serum level of Smac was reduced 2-fold in bladder cancer patients in comparison with normal donors. The mean serum level of Smac either was reduced in patients with an advanced stage and grade tumor. Lower serum level of smac predicted early recurrence in patients with bladder cancer (Mizutani et al., 2012).

Breast cancer

Note

Smac expression is reduced in breast cancer and inversely correlates with the tumor stage (Pluta et al., 2011). Smac expression is more prevalent in the HER2 positive group than negative group (Zhang et al., 2011). Additonally, Smac mRNA expression is downregulated in breast cancer samples and shows an inverse correlation with survivin mRNA expression (Mansour et al., 2012).

Endometrioid endometrial cancer

Note

Smac protein expression correlates with tumor grade. Negative expression of Smac is a sign of poor prognostic in this kind of tumor (Dobrzycka et al., 2010).

Ovarian mucinous tumor

Note

Smac protein expression is downregulated in this tumor. Smac expression inversely correlates with Survivin expression. Analysis of subcellular localization of Smac demonstrate that Smac protein exist mainly in the intermembranal space of the mitochondria (Wang et al., 2010).

Lung cancer

Note

Smac mRNA expression is lower in primary lung cancer than in normal tissues. In squamous cell carcinomas the expression of Smac is more reduced than in adenocarcinomas. In tumours of smokers the expression of Smac mRNA is lower than in tumours of non smokers. Smac expression correlates inversely with stage tumour and low expression is sign of worse prognostic (Sekimura et al., 2004).

Non-small cell lung cancer

Note

Smac mRNA expression is significantly increased in NSCLC tissues in comparison with lung tissue (Krepela et al., 2006). In advanced NSCLC high smac mRNA expression correlates with longer progression-free survival (PFS) and overall survival (OS). Smac is an independent prognostic factor for OS, but not for FPS (Chen et al., 2010).

Prostate cancer

Note

Smac protein is increased in prostate cancer and correlates with high Gleason score (sum=8-10) (Grubb et al., 2009).

Colorectal cancer

Note

Patients with smac-negative cancer have higher incidence of lymph node and distant metastases than smac positive-cancer. Negative expression of Smac predicts poorer survival and is a prognostic indicator independent of Duke's staging and lymph node metastases (Endo et al., 2009).

Testicular germ cell tumours

Note

Smac mRNA is downregulated during the development and progression of TGCT. While Smac mRNA is downregulated XIAP mRNA expression is unchanged, and patients with high ratio XIAP:Smac are likely in clinical stage III (Kempkensteffen et al., 2007; Kempkensteffen et al., 2008b).

Mycosis fungoides

Note

The 12q24.31 region is frequently deleted in early stages of MF (Carbone et al., 2008).

Disease

The most frequent form of cutaneous T cell lymphoma.

Renal cell carcinoma

Note

Smac protein expression is downregulated in RCC and no expression of Smac predicts a worse prognosis (Mizutani et al., 2005). Either Smac mRNA expression is inversely associated with outcome of RCC patients (Kempkensteffen et al., 2008a).

Cervical cancer

Note

Smac mRNA is expressed de novo in cervical cancer, although no correlation with any clinical variable was found (Espinosa et al., 2004). However, Smac protein expression correlates with microvascular density, a marker for angiogenesis (Arellano-Llamas et al., 2006).

B-cell non-Hodgkin and Hodgkin lymphomas

Note

Smac protein is expressed in almost fifty percent of NHL and HL tissues. Smac protein is differentially expressed in various NHL types while all HL types were positive for Smac (Ren et al., 2006).

Acute leukemia (AL)

Note

Smac mRNA expression is increased in de novo AL patients in comparison with normal controls and the levels decrease in patients at complete remission. In relapsed patients the levels of Smac are increased

again. Smac expression in AL is related to remission rate, patients with high levels of Smac have low remission rates. Smac expression could serve like a marker of prognosis in AL (Wang and Zhou, 2006).

Chronic lymphocytic leukemia (CLL)

Note

An increased expression of Smac has been observed in CLL samples. Possibly, these high levels of Smac in CLL could prevent the inhibitory effect of XIAP on caspases, since in conditions where XIAP is upregulated and apoptosis is prevented, there's no caspase inhibition (Schliep et al., 2004; Winkler et al., 2005). However, downregulation of Smac has been also observed in CLL samples. Higher expression of IAPs and lower levels of Smac were found in patients with progressive disease, compared with those with stable CLL (Ren et al., 2006; Grzybowska-Izydorczyk et al., 2010).

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