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Gene Section

Review

NOL3 (nucleolar protein 3 (apoptosis repressor with CARD domain))

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Identity

Other names: ARC (Apoptosis Repressor with CARD); CARD2; MYP; NOP; NOP30

HGNC (Hugo): NOL3

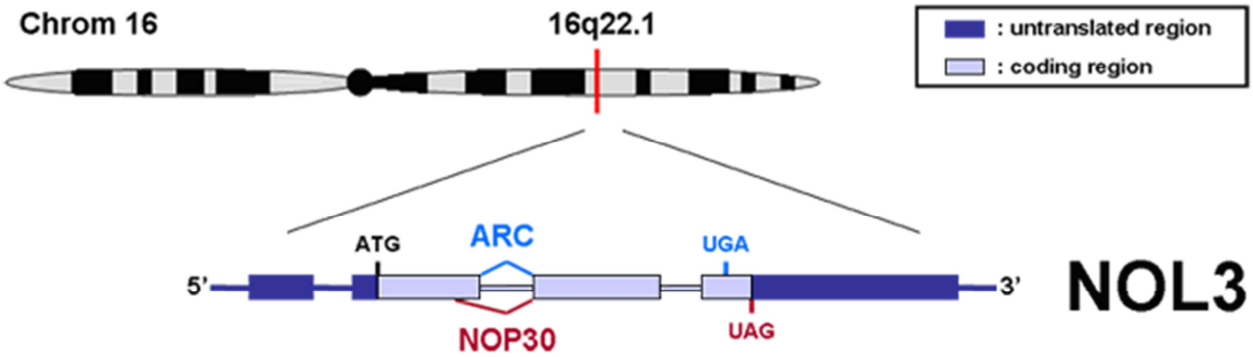
Location: 16q22.1

Note

The correct name for the locus is NOL3. Sometimes, however, the gene is referred to by names of the putative encoded proteins:

ARC (Apoptosis Repressor with CARD) CARD denotes a Caspase Recruitment Domain. The ARC protein resides in the cytoplasm and nucleoplasm, not nucleolus.

MYP is an older name for ARC that is currently not used. References to this locus as MYC are incorrect and probably represent typographical errors of MYP. NOL3 is distinct from any of the myc loci.



The NOL3 gene is located on the long arm of human chromosome 16. The gene consists of 4 small exons (exons denoted above as thick boxes) and 3 small introns. The translational start site is in exon 2. Alternative splicing occurs between exons 2 and 3. This involves two splice donors separated by 10 nucleotides in exon 2 connecting to a single splice acceptor in exon 3 (Stoss et al., 1999). Because the separation between the splice donors, 10 nucleotides, is not an exact multiple of 3, alternative splicing results in two open reading frames distal to the splice acceptor. Because of this frame shift, the C-terminus of the two encoded proteins differ as do their stop codons, each of which is in exon 4. One transcript is translated into ARC (Apoptosis Repressor with CARD (Caspase Recruitment Domain)) (Koseki et al., 1998). MYP is an earlier name for ARC that is no longer in use (Geertman et al., 1996). The other transcript encodes a putative protein called NOP30 (Nucleolar Protein of 30 kD). ARC and putative NOP30 proteins share a common N-terminus containing the CARD. Their C-termini differ, however, with ARC containing multiple P/E repeats (acidic) and putative NOP30 containing R/S repeats (basic). While ARC transcripts are present in a variety of human and mouse cell types, NOP30 transcripts are present in human, but not mouse (L. Wu and R. Kitsis, unpublished). Endogenous ARC protein resides in the cytoplasm and nucleoplasm of certain human and mouse cell types (discussed below). In contrast, the existence of endogenous NOP30 protein has not been demonstrated in any cell type of any species. When the cDNA encoding NOP30 is exogenously expressed, the encoded protein is in the nucleolus and nucleoplasm (Stoss et al., 1999).

NOP30. In some species, alternative splicing gives rise to a transcript encoding a putative protein NOP30, rather than ARC. When the cDNA for NOP30 is expressed exogenously, the resulting protein is predominantly nucleolar - hence the origin of the gene name: nucleolar protein 3. Impo-rtantly, however, endogenous NOP30 protein has not been demonstrated in any cells of any species.

DNA/RNA

Description

The NOL3 gene is located on human chromosome 16q21-23. The gene contains 4 exons and 3 introns spanning 1757 bp.

Transcription

The coordinate of the first nucleotide of exon 1 is 65,765,371 bp from pter, and that of the last nucleotide of exon 4 is 65,767,127 bp. Alternative splicing takes place between exons 2 and 3. In exon 2, the splice donor of the NOP30 transcript is 10 bp upstream of the splice donor of the ARC transcript. Both transcripts use a common splice acceptor in exon 3.

Protein

Note

The start of translation is in exon 2 (prior to the alternative splice donors). Alternative splicing causes a frame shift resulting in transcripts encoding proteins with different C-termini and separate stop codons in exon 4. The stop codon for ARC is 43 bp upstream of that of NOP30.

Alternatively spliced transcripts of NOL3 lead to two different proteins, ARC (blue) and NOP30 (red). These proteins each contain an N-terminal CARD (first 95 amino acids identical), but have different C-termini. The C-terminus of ARC is rich in prolines and glutamic acids, whereas the C-terminus of NOP30 is rich in serines and arginines.

Description

Human ARC protein contains 208 amino acids with M_r 22,629 Da. The protein usually runs at a slower mobility on SDS-PAGE most likely due to the enrichment of proline residues in the C-terminal domain. NOP30 contains 219 amino acids with M_r 24,327 Da.

Expression

Under normal conditions, ARC mRNA and protein is present predominantly in cardiac myocytes, skeletal myocytes, and neurons (Koseki et al., 1998; Abmayr et al., 2004; Geertman et al., 1996; Engidawork et al., 2001). ARC protein is also markedly increased in primary human epithelial cancers of the breast, colon, ovary, and cervix (Mercier et al., 2005; Mercier et al., 2008). NOP30 transcripts are present in some human cell types but have not been detected in mouse cells. Endogenous NOP30 protein has not been demonstrated in cells of any species.

Localisation

Endogenous ARC protein is present in the cytoplasm and nucleoplasm (Mercier et al., 2005). As above, the localization of endogenous NOP30 protein has not been investigated. Exogenously expressed NOP30 protein localizes in the nucleolus and nucleoplasm.

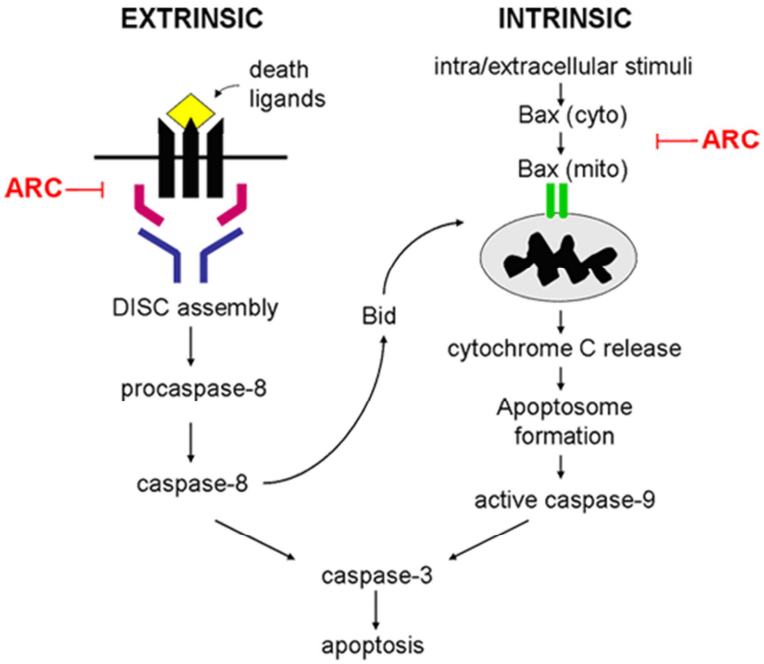
Function

The function of endogenous NOP30 is not known. Exogenous NOP30 interacts with SFRS9/SRp30C and NPM1 and may influence splicing (Stoss et al., 1999).

ARC is an endogenous inhibitor of apoptosis that is unique in its ability to antagonize both the extrinsic (death receptor) and the intrinsic (mitochondria/ER) death pathways (Nam et al., 2004; Gustafsson et al., 2004; Koseki et al., 1998). ARC inhibits the extrinsic pathway by interfering with DISC (Death Inducing Signaling Complex) formation. This is accomplished by the direct interaction of the ARC CARD with the death domains (DD) of Fas and FADD, and with the death effector domain (DED) of procaspase-8. These death-fold interactions are novel in that they are heterotypic in contrast to the usual homotypic death-fold interactions. ARC inhibits the intrinsic pathway through at least two mechanisms. First, the direct interaction between the ARC CARD and the C-terminus of Bax inhibits death stimulus-induced Bax conformational activa-tion and translocation to the mitochondria. Second, direct interaction between the ARC C-terminal domain with the p53 tetramerization domain inhibits p53 tetramerization (Foo et al., PNAS, 2007). This, in turn, disables p53 transcriptional function and exposes a p53 nuclear export signal that relocates p53 to the cytoplasm.

Nothing is known about the regulation of NOP30.

The regulation of ARC is complex. ARC protein abundance decreases rapidly and dramatically in response to hypoxia and oxidative stress (e.g. ischemia-reperfusion) (Ekhterae et al., 1999; Neuss et al., 2001; Nam et al., 2007). These decreases result from increased degradation of ARC protein via the ubiquitin-proteasomal pathway (Nam et al., 2007). The E3 ligase MDM2 may play a role in ARC degradation in this scenario (Foo et al., JBC, 2007), but this role is probably indirect (L. Wu and R. Kitsis, unpublished data). Decreases in ARC protein abundance in response to hypoxia appear to be regulated by p53 repression of nol3 transcription (Li et al., 2008). Apart from ARC protein abundance, the activity of ARC is also regulated



Regulation of the extrinsic (death receptor) and intrinsic (mitochondria/ER) apoptosis pathways by ARC. Not shown are ARC interactions with and regulation of p53.

post-translationally: dephosphorylation of threonine 149 decreases the anti-apoptotic activity of ARC (Tan et al., 2008).

Homology

ARC is highly conserved among mammals. There is approximately 85% identity both at the amino acid and the nucleotide level among human, rat, mouse, dog, and bovine ARC. Interestingly, an ARC homolog has yet to be identified in Danio rerio, Drosophila melanogaster, or Caenorhabditis elegans.

Implicated in

Epithelial cancers

Disease

Increased levels of ARC protein have been observed in the epithelium of primary human breast, colon, ovarian, and cervical cancers (Mercier et al., 2005; Mercier et al., 2008). Increased levels of both ARC RNA and protein have been observed in renal cell carcinoma (Heikaus et al., 2008).

Prognosis

ARC overexpression in a breast cancer cell line increases resistance to chemotherapy and radiation (Mercier et al., 2005; Wang et al., 2009). In a mela-noma cell line, ARC overexpression causes increased resistance to endoplasmic reticulum stress-induced caspase-8 activation (Chen et al., 2008).

Myocardial infarction, myocardial ischemia-reperfusion

Prognosis

ARC plays an important role in regulating heart muscle damage during myocardial infarction. Endogenous ARC protein undergoes rapid protea-somal degradation during myocardial ischemia-reperfusion (Nam et al., 2007). This decrease in ARC abundance is causally linked with the subsequent cell death (Nam et al., 2004). Accordingly, transgenic overexpression of ARC in vivo decreases the size of myocardial infarctions (Gustafsson et al., 2002; Pyo et al., 2008; S. Jha and R. Kitsis, unpublished data). As would be predicted, knockout of ARC has been reported to result in larger infarcts (Donath et al., 2006). However, the aforementioned knockout studies were performed on only small numbers of mice on a mixed genetic background. Subsequent knockout studies involving large numbers of mice on several pure genetic backgrounds have not demonstrated larger infarcts in ARC-/- mice subjected to ische-mia-reperfusion (J. Saurabh, S. Y. Ji, and R. Kitsis, unpublished data). This is probably due to the dramatic rapid degradation of ARC protein during reperfusion even in wild type mice (see above).

Heart failure

Prognosis

ARC protein levels decrease during heart failure. Moreover, knockout of ARC exacerbates patholo-gical cardiac remodeling in response to hemody-namic overload, a model of heart failure (Donath et al., 2006).

Neuropathology (several individual entities)

Prognosis

The protein level of ARC is increased in the frontal cortex of patients with Alzheimer's disease

(Engidawork et al., 2001). During ischemic injury of the brain, there is a decrease in ARC protein in hippocampal neurons (Hong et al., 2003). Other studies have also shown that caloric restriction increases expression of ARC in the brain (Shelke et al., 2003).

Breakpoints

Note
Not known.

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