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Gene Section
Short Communication

ROS1 (ROS proto-oncogene 1 , receptor tyrosine kinase)

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Abstract

ROS1 is proto-oncogene encoding a type I integral membrane protein with receptor tyrosine kinase (RTK) activity.
ROS1 is a member of the insulin receptor family and is involved in downstream signalling processes involved in cell growth and differentiation.

Keywords
ROS1; tyrosine kinase; insulin receptor family; cell growth and differentiation; cancer

Identity

Other names: c-ros-1, MCF3, ROS

HGNC (Hugo): ROS1

Location: 6q22.1

Note
ROS1 is proto-oncogene encoding a type I integral membrane protein with receptor tyrosine kinase (RTK) activity.
ROS1 is a member of the insulin receptor family and is involved in downstream signalling processes involved in cell growth and differentiation.

DNA/RNA

Description

The ROS1 gene is highly conserved from drosophila through zebrafish, rat, cow, rhesus, and homo sapiens. Refseq NM_002944.

Protein

Description

ROS1 gene encodes a 2,347 amino acid protein with a molecular weight of 263,915 Daltons (NCBI: P08922). This protein is a type I single pass integral membrane protein with tyrosine kinase activity. SwissProt identifier P08922, Protein NP_002935

Expression

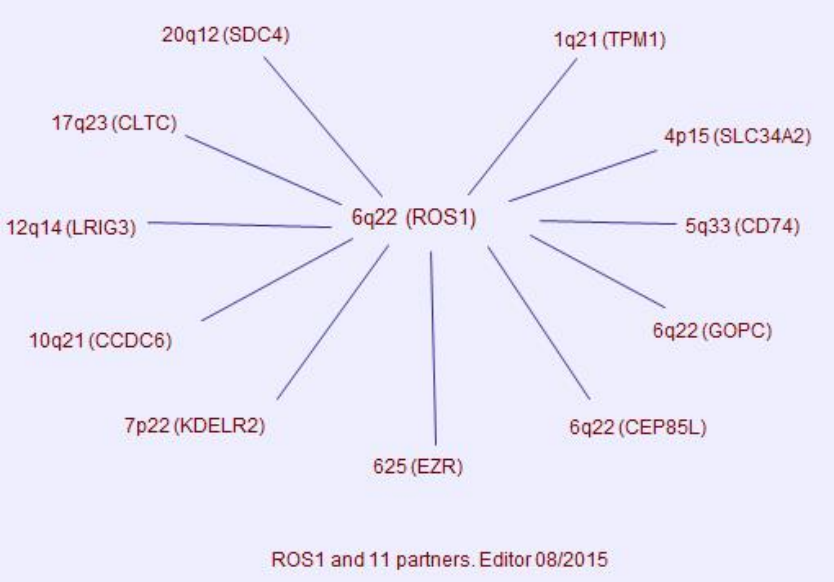
ROS1 expression is involved in regionalization of the proximal epididymal epithelium. Expression levels have been highest in liver, platelelts, T-cells and monocytes, but is found across nearly all cell types.

Localisation

ROS1 is localized to the cell plasma membrane and contains both extracellular and intracellular domains.

Function

ROS1 functions as an orphan receptor tyrosine kinase with an unestablished ligand. ROS1 directly interacts via an SH2 1 domain with PTPN6 which drives ROS1 dephosphorylation (Charest et al., 2006). ROS1 has also been suggested to interact with PTPN11 leading to PI3K/mTOR signaling, and to mediate phosphorylation of VAV3 (Charest et al., 2006). The ligand for wild type ROS1 is unknown and the normal function remains unclear despite the above associations.



Homology

ROS1 shares significant homology with other members of the insulin growth factor receptor family, and the gene is highly conserved back through drosophila melanogaster.

Mutations

Germinal

None established.

Somatic

The intrachromosomal del(6)(q21q22) deletion has been identified in glioblastoma multiforme and leads to the formation of a constitutive active GOPC-ROS1 protein (Charest et al., 2003). In non-small cell lung cancer (NSCLC) the SLC34A2-ROS1 chimeric protein also holds kinase activity. A CD74-ROS1 chimeric protein has also been identified in NSCLC (Awad et al., 2013).

Implicated in

Non-small cell lung cancer, renal oncocytoma, gastric cancer, glioblastoma multiforme, cholangiocarcinoma colorectal cancer.

Note

There has been a rapidly expanding appreciation of ROS1 fusion proteins in the tumorigenesis of multiple malignancies as discussed below (Charest et. al., 2003, Gu et al., 2011, Rimkunas et al., 2012, Takeuchi et al.,2012, Awad et al., 2013, Lee et al., 2013).

Disease

ROS1 rearrangements occur in <2% of NSCLC and are enriched for in adenocarcinoma and young never smokers (Bergethon et al., 2012).

Prognosis

To date ROS1 has not been clearly implicated as an independent prognostic variable. ROS1 rearrangements may predict sensitivity to the ALK-inhibitor Crizotinib in NSCLC. Small molecule inhibitor screens have also identified foretinib as a potent inhibitor of multiple ROS1 fusion proteins. Additionaly, ROS1 mutation has been observed as a acquired resistance mechanism to crizotinib. Davare and colleagues have shown that foretinib is capable of inhibiting the G2032R ROS1 mutant which is resistant to crizotinib (Davare et al., 2013).

Cytogenetics

ROS1 rearrangements have been documented with the following fusion partners; CCDC6, CD74, CEP85L, also called C6orf204, CLTC, EZR, GOPC, KDELR2, LRIG3, SDC4, SLC34A2, and TPM3.

Translocations and fusion proteins: t(1;6)(q21;q22) TPM3/ROS1; t(4;6)(p15;q22) SLC34A2/ROS1; t(5;6)(q33;q22) CD74/ROS1; t(6;6)(q22;q22) GOPC/ROS1; t(6;6)(q22;q22) CEP85L/ROS1; t(6;6)(q22;q25) EZR/ROS1; t(6;7)(q22;p22) KDELR2/ROS1; t(6;10)(q22;q21) CCDC6/ROS1; t(6;12)(q22;q14) LRIG3/ROS1; t(6;17)(q22;q23)CLTC/ROS1; t(6;20)(q22;q12) SDC4/ROS1 (Charest et. Al., 2003, Gu et al., 2011, Rimkunas et al., 2012, Takeuchi et al., 2012, Awad et al., 2013, Lee et al., 2013, Mitelman et al., 2015). Within NSCLC ROS1 rearrangements are non-overlapping with EGFR, KRAS, and ALK genomic

alterations (Davies et al., 2012, Awad et al., 2013, Go et al., 2013).

Breakpoints

Note

Within the COSMIC database ROS1 chromosomal rearrangements have been documented with the following fusion partners ; CD74, EZR, GOPC, SDC4, TPM3, SLC34A2, and LRIG3 (COSMIC, accessed 12/2013).

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