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Gene Section

Review

RAC2 (ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2))

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Identity

Other names: EN-7; GX; Gx; HSPC022; p21-Rac2

HGNC (Hugo): RAC2

Location: 22q13.1

DNA/RNA

Description

The Rac2 gene sequence contains 7 exons (Courjal et al., 1997) and is expressed specifically in hematopoietic cells. Human Rac2 gene locus is silenced in non-hematopoietic cells by a mechanism that involves DNA methylation (Ladd et al., 2004). Cells that lack Rac2 expression exhibit increased cytosine methylation in the sequences flanking the gene, whereas cells that express Rac2 exhibit increased cytosine methylation within the body of the Rac2 gene.

Transcription

The human Rac2 gene promoter lacks TATA and CCAAT boxes, utilizes multiple transcription initiation sites, and contains several putative Sp1 binding sites, which is common in promoters that lack TATA boxes (Ladd et al., 2004).
The transcript length is of 1471 nt translated to a 192 residues protein.

Protein

Description

Rac2 protein belongs to the GTP-binding proteins of the Rho family and cycles between an active GTP-bound form and an inactive GDP-bound form.

This regulatory cycle is exerted by three distinct families of proteins: guanine exchange factors (GEFs), GTPase-activating proteins (GAPs), and guanine nucleotide dissociation inhibitors (GDIs). Several GEFs have been shown to activate Rac2 selectively, Vav1 (Ming et al., 2007), Tiam1 (Haeusler et al., 2003), P-Rex1 (Welch et al., 2002), Swap70 (Sivalenka and Jessberger, 2004) and Dock2 (Nishihara et al., 2002). Two GAPs that act on Rac2 are Abr and Bcr (Chuang et al., 1995), as well as others found in leukocytes.
Rac2 function depends on association of the GTPase with membranes and subcellular localization, properties influenced by C-terminal lipid modifications, specifically is modified by the C20 GG isoprenoid.
Upon GTP loading, a conformational change takes place that allows Rac2 protein to interact with several downstream effectors that ultimately process the information and propagate the signal within the cell, causing changes in the actin cytoskeleton, release of inflammatory modulators and innate immunity. The signaling of active Rac2 is mediated by its interaction with effector proteins such as p67phox and cytochrome b-558 (Diebold and Bokoch, 2001), PLCbeta2 (Piechulek et al., 2005), nitric oxide synthase 2 (NOS2) (Kuncewicz et al., 2001) and Pak1 (Carstanjen et al., 2005).

Expression

Expression is restricted to hematopoietic cells and exhibits the highest expression in myeloid cells. Rac2 expression is regulated during the differentiation of hematopoietic and myeloid cells. There is some data suggesting that Rac2 might be expressed in tumors.

Localisation

Once activated Rac2 is mainly localized in endomembranes.

Function

As suggested by its restricted expression, Rac2 has a specialized role in many hematopoietic and immunological processes. Rac2 deficient mice show defects in stem cells, mast cells as well as B and T cells.

Role in hematopoietic stem-cell progenitor engraftment

The contribution of the GTPase Rac2 to the normal functioning of hematopoietic stem-cell progenitors (HSC/Ps) was addressed based on the phenotype of Rac2-/- mice (Gu et al., 2003). HSC/Ps from these mice showed normal short-term engraftment, but decreased adhesion, suggesting a key role for Rac2 in integrin-mediated stem-cell adhesion. In addition, Rac2-/- HSC/Ps formed colonies with both impaired growth and migration, and showed an increased rate of apoptosis.

In response to stromal derived factor 1, Rac2-/- cells failed in cortical F-actin assembly, and presented reduced cell spreading and actin-based membrane protrusion.

Role in neutrophils function

Several reports point out Rac2 is the predominant Rac GTPase functioning in neutrophils. These observations came from studies in neutrophils from Rac2-/- mice and a patient with a dominant-negative Rac2 mutation in which these cells showed decreased motility, adhesion, major defects in cortical F-actin assembly, and accordingly, chemotaxis and reduced phagocytosis and superoxide production by NAPH oxidase (Williams et al., 2000; Roberts et al., 1999; Li et al., 2002; Gu et al., 2003). Rac2 is required for oxidase activity through its direct interaction with p67-phox and cytochrome b 558.

Role in B-cell development

Rac2-/- mice exhibit multiple defects in B-cell development, with reduced numbers of peripheral blood B-cells and IgM-secreting plasma cells, a severe reduction in the number of marginal zone and peritoneal B1 cells (Croker et al., 2002). Rac2 participates in the positive selection through the B-cell receptor (BCR), since is activated by BCR cross-linking (Grill and Schrader, 2002).

Role in T-cell differentiation

Rac2 activity is required for interferon-gamma (IFNgamma) production both in vitro and in vivo during normal T-cell activation and Th1-cell differentiation, through simultaneous activation of both the NFkappaB and p38 pathways (Li et al., 2000).

Role in Mast cell survival

The absence of Rac2 results in defects growth, survival, chemotaxis, adhesion, and degranulation in mast cell (Yang et al., 2000). Rac2 is critical in regulating the growth factor-induced survival through activation of Akt and a change in expression levels of the Bcl-2 family members BAD and Bcl-XL (Yang et al., 2000).

Homology

Rac2 share significant sequence identity (~88%) with the other two members of the subfamily Rac: Rac1 and Rac3. The three proteins diverge primarily in the C-terminal 15 residues. Regarding to the biochemical properties, Rac2 shows a slower nucleotide association and is more efficiently activated by the Rac-GEF Tiam1 than Rac1 and Rac3.

Mutations

Note

POLYMORPHISMS

Two single nucleotide polymorphisms (SNP) have been observed in gliomas (Idbaih et al., 2008). The SNPs rs2239774 in exon 2 (codon 27, GCC to GCG, Ala to Ala) and rs3179967 in exon 6 (codon 159, GCT to GCC, Ala to Ala) were observed in 15/78 and 7/78 cases, respectively. No association between these two SNPs with phenotype, tumor grade, patient age, and patient gender was seen.

Germinal

A point mutation has been identified in one allele of the Rac2 gene resulting in the substitution of Asp57 by an Asn ($Rac2^{D57N}$) in a patient with a primary immunodeficiency syndrome (Ambruso et al., 2000; Williams et al., 2000). Rac2D57N binds GDP but not GTP and inhibits oxidase activation and superoxide production in vitro.

Somatic

So far only two studies have searched for the presence of somatic mutations, both of them analyzed human brain tumors. Hwang et al. found 26% of cases had Rac2 gene mutation, two cases with decreased Rac2 expression and four cases with normal Rac2 expression. One case showed the mutation site nearby the GTP-binding site, which may affect Rac2 GTPase activity, but the site of Rac2 mutation seems not to concentrate in the effector region. However, Idbaih et al. did not find missense mutations in a series of 78 gliomas.

Implicated in

Immunodeficiency

Disease

Lack of Rac2 activity causes immunodeficiency (Ambruso et al., 2000; Williams et al., 2000). A single patient was identified with a primary immunodeficiency syndrome resulting from a heterozygous mutation in the Rac2 gene. In the first 5 months after birth, the patient presented several bacterial infections, poor wound healing, and absence of pus in the wounds, indicative of a phagocyte defect. The neutrophils had decreased chemotactic motility, polarization, and secretion of azurophilic granules.

Rac2 levels were reduced, suggesting a defect in this GTPase. Western blot analysis of lysates from patient neutrophils demonstrated decreased levels of Rac2 protein. Molecular analysis identified a point mutation in one allele of the Rac2 gene resulting in the substitution of Asp57 by an Asn ($Rac2^{D57N}$). Rac2D57N inhibits oxidase activation and superoxide production in vitro. These data represent the description of an inhibitory mutation in a member of the Rho family of GTPases associated with a human immunodeficiency syndrome.

Brain tumors

Oncogenesis

Expression of Rac2 was examined by RT-PCR and Northern blotting in human brain tumors: 10 astrocytomas, 8 meningiomas, and 8 pituitary adenomas (Hwang et al., 2005). The overexpression of Rac2 was evident in 1/10 astrocytomas and 1/8 meningiomas. No overexpression was found in pituitary adenomas. The decreased expression of Rac2 was found in 15 of 26 brain tumors (8/10 astrocytomas, 2/8 meningiomas and 5/8 pituitary adenomas).

Head and neck squamous cell cancer

Oncogenesis

Western blot analysis showed increased expression of Rac2 in a malignant squamous cell cancer cell line and a premalignant dysplastic cell line compared to the normal human epidermal keratinocytes (Abraham et al., 2001). This observation was confirmed with an immunohistochemical study of 15 moderately to poorly differentiated head and neck squamous cell cancer specimens, where a specific increased expression of Rac2 in areas of squamous cell cancer compared to the normal tissue was observed. Rac2 shows nuclear staining in normal human epidermal keratinocytes increasing sequentially in premalignant and malignant cell lines. In addition, there is specific cytoplasmic staining of the malignant cancer cell line which is absent in the normal and premalignant cell lines. This differential cytoplasmic staining may be able to distinguish invasive squamous cell carcinoma from dysplastic lesions and benign normal mucosa. Consequently it has been proposed that this GTPase could have an important role in the diagnosis and staging of this tumor type.

Acute myeloid leukemia (AML)

Oncogenesis

Activating mutations of KIT, which encodes the receptor for the cytokine stem cell factor, have been described in acute myeloid leukemia. Genetic disruption of Rac2 or pharmacologic evidence through treatment with Rac inhibitor NC23766, implicate Rac2 in regulating KIT-induced transformation in acute myeloid leukaemia (Munugalavadla et al., 2007). These results suggest Rac2 as a potential novel therapeutic target for the treatment of KIT-bearing acute myeloid leukemia.

Chronic myelogenous leukemia (CML)

Oncogenesis

Gene targeting of Rac1 and Rac2 significantly delays or abrogates development of chronic myelogenous leukemia (CML), a clonal myeloproliferative disease (MPD) initiated by expression of the p210-BCR- ABL fusion protein (Thomas et al., 2007). These genetic data were further substantiated experimentally by use of NSC23766, small molecule antagonist of Rac activation, to validate biochemically and functionally Rac as a molecular target in both a relevant animal model and in primary human CML cells in vitro and in a xenograft model in vivo. These findings indicate that Rac GTPases are critical for p210-BCR-ABL-mediated transformation and, therefore, suggest that the Rac GTPases may prove to be useful therapeutically by targeting alternative signaling pathways, which may be responsible for resistance and relapse in CML.

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