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Gene Section
Review

RAB31 (Ras-related protein in brain 31)

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Abstract

Rab31 is a member of the large Rab protein family (66 human members) of the Ras superfamily of small GTPases. Rab31 is expressed fairly ubiquitously in normal human tissue and regulates membrane traffic between the Golgi/TGN and the plasma membrane and/or endosomes. Dysregulated expression of Rab31 has not only been observed in several types of cancer, including breast, ovarian, cervical and liver cancer as well as glioblastoma, but also in skin diseases such as psoriasis and atopic dermatitis.

Keywords
GTPase, Rab22b, trans-Golgi network, endosome, vesicle transport, clinical relevance

Identity

Other names: RAB22B

HGNC (Hugo): RAB31

Location: 18p11.22

DNA/RNA

Note

Cloning: A human cDNA encoding for Rab31 was first isolated in 1996 (Chen et al. 1996, Bao et al. 1996). Chen et al. (1996) isolated a cDNA encoding for a novel human Rab protein from a human melanocyte cDNA library and human melanocytes. Since its sequence showed a significant homology to canine Rab22 it was named Rab22B. A BLAST analysis revealed that Rab22B shared 71% identity and 82% similarity with canine Rab22.

Around the same time, Bao et al. (1996, 1997) identified a cDNA encoding for a previously unknown human Rab protein in human platelets. Because the accepted guideline for the use of the next available Rab numbers at that time was an identity less than 85%, the new protein was named Rab31 instead of Rab22B (Chen et al. 1996; Bao et al. 2002).

Rodriguez-Gabin et al. (2001) identified a Rab sequence (rRab22B) cloned from a rat oligodendrocyte cDNA library with a high identity to human Rab31. Since comparison of the rRab22B sequence with human Rab31 (on the protein level) showed 88% identity it has been suggested that rRab22b encodes the rat homolog of human Rab31. In view of the fact that a segment of the carboxy-terminal domain shows 9 differences among the last 18 residues, one must, however, consider that rRab22B (and also murine Rab22B which is 97.9% identical with rRab22B) still may encode a new member of the Rab family, especially, because the carboxy-terminal end is part of the motif responsible for the targeting of Rab proteins to specific membrane compartments (Rodriguez-Gabin et al. 2001). Despite of this notion the authors refer to rRab22B as Rab31 (Rodriguez-Gabin et al. 2009).

Description

DNA size: 154,326, 7 exons (Fig. 1)

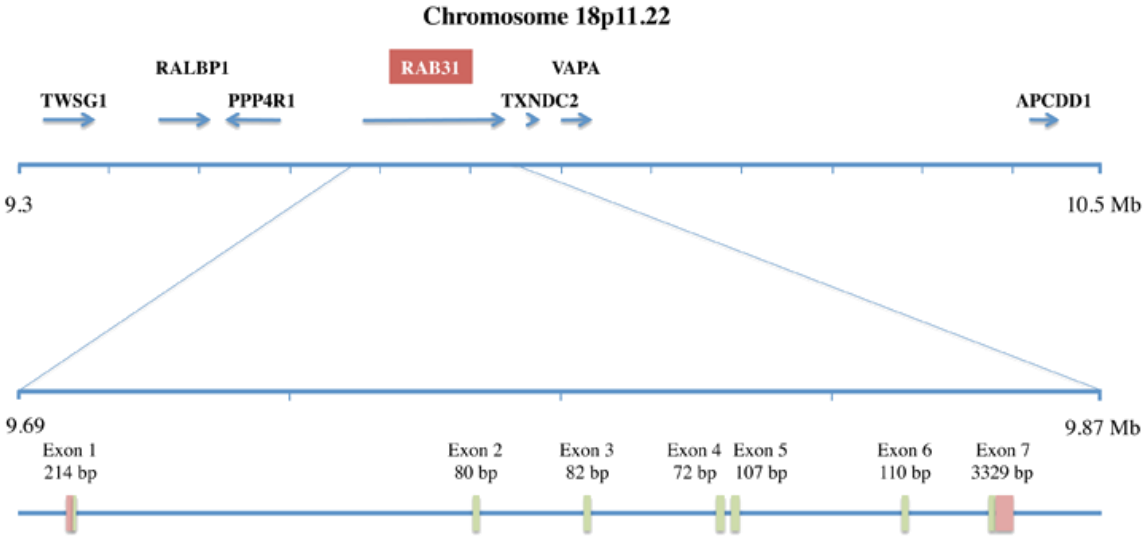


Figure 1. Location of the Rab31 gene (RAB31) on chromosome 18p11.22 The introns dividing the seven exons display following phases: I^{E1-2}: 0; I^{E2-3}: 2; I^{E3-4}: 0; I^{E4-5}: 0; I^{E4-5}: 2; I^{E6-7}: 1. The intron phases between RAB31 and its closest homolog RAB22A, located on chromosome 20, are conserved.

Protein

Description

The coding sequence of human Rab31 corresponds to a 194 amino acid (aa) protein with a nominal molecular mass of 21.6 kDa and a pI of 6.7.

The crystal structure of human Rab31 bound to a non-hydrolyzable GTP analog, guanosine-5'-(β γ)-imidotriphosphate (GppNHp) at 2.8 Å was described by Tempel et al. (2006) and is presented in Fig. 2A.

Rab31 possesses a typically GTPase fold, composed of a six-stranded β-sheet core flanked by five α-helices. The binding site for guanine nucleotides and Mg^{2+} is well conserved among Rab proteins (Fig. 2B; aa 12-19, 60-64, and 118-121). The GTPase fold is followed by a hypervariable region, which harbors two cysteine residues to which geranylgeranyl moieties are covalently attached. Modification by geranylgeranylation is required for its proper subcellular localization, mainly the trans-Golgi network (Chua and Tang 2015).

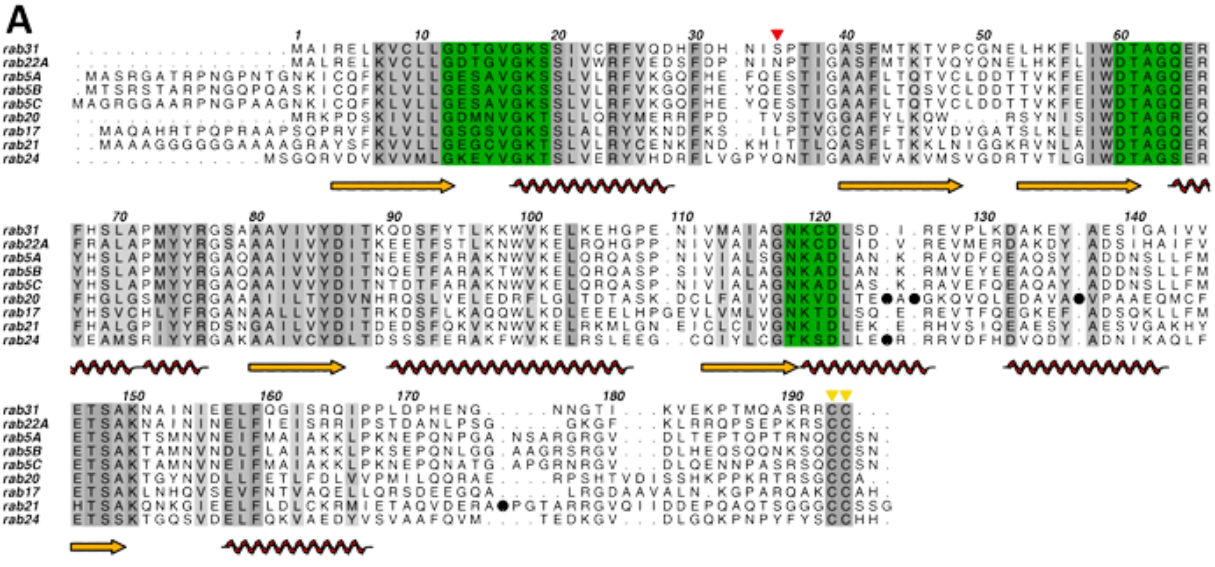
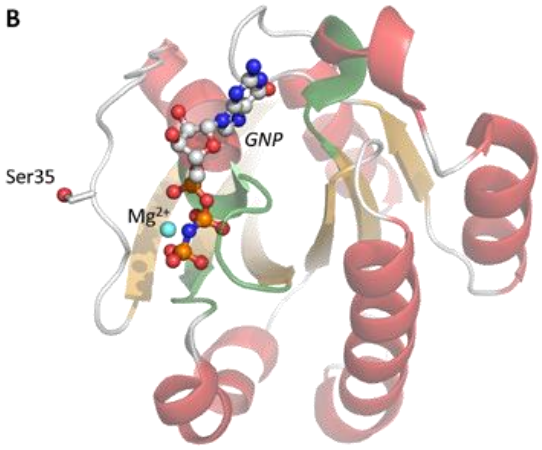


Figure 2. Primary and tertiary structure of Rab31 (A) Sequence alignment of Rab31 and the other members of the so-called group II of the human Rab family (Klöpper et al. 2012). Secondary structure is shown for Rab31 for β-strands (yellow arrows) and α-helices (red helices). Highly conserved residues are displayed with a grey background, the composite binding sites for guanine nucleotides and Mg^{2+} is (aa 12-19, 60-64, and 118-121 of Rab31) are marked with a green background. Ser35 (indicated by a red triangle) has been mapped as phosphorylation site (www.phosphosite.org). The C-terminal region (~ 30 aa) is hypervariable except the two invariant cysteine residues to which geranylgeranyl moieties are post-translationally attached for membrane association. Black dots within the sequences of Rab17, 20, 21, and 24 indicate unique larger insertions not present in the other Rab proteins of the group II superfamily.



(B) Crystal structure of human Rab31 bound to the non-hydrolyzable GTP analog GppNHp/ GNP (Tempel et al. 2006). β-strands are indicated in yellow, α-helices in red; the composite binding site for guanine nucleotides and Mg^{2+} (cyan sphere) is marked in green. The side chain of Ser35, which is a target for phosphorylation is indicated as well. The two C-terminal cysteines, which are modified by prenylation, are not defined in the crystal structure.

Expression

Non-malignant tissue. Rab31 is expressed fairly ubiquitously in normal human tissue. At the transcript level, highest expression of Rab31 was found in testis, ovary, small intestine, brain, placenta, lung, adrenal gland, urinary bladder, endometrium, and smooth muscle (Chen et al. 1996; Bao et al. 2002; Human Protein Atlas: www.proteinatlas.org, Uhlén et al. 2015). High or medium protein expression levels of Rab31were detected by immunohistochemistry in 35 of 45 analyzed non-malignant tissue types (Human Protein Atlas).

Cancer tissue. Highest Rab31 immunoexpression was observed in malignant tissue of glioma, breast, and thyroid cancer as well as melanoma (Human Protein Atlas).

Localisation

Most normal cells display weak to moderate cytoplasmic staining, in a few cases of peri-nuclear staining (Human Protein Atlas). Within the cytoplasm, Rab31 was shown to be localized mainly in the Golgi, the trans-Golgi network (TGN) and endocytic compartments (Rodriguez-Gabin et al. 2001).

Function

The members of the Rab family of small GTPases regulate various steps of dynamic assembly and disassembly of multi-protein scaffolds, which are involved in vesicular traffic in both endocytic and secretory pathways. Rab31 regulates anterograde ("inside-out") and retrograde ("outside-in") membrane traffic between the Golgi/TGN and the plasma membrane and/or endosomes.

Rab proteins cycle between two alternate conformational states, inactive (GDP-bound) and active (GTP-bound) (Fig. 3).

The activity of the Rab proteins is controlled by several regulatory factors: (i) Rab escort proteins (REPs), which transport newly synthesized Rab proteins to geranylgeranyl transferases for C-terminal prenylation enabling specific membrane association; (ii) guanine exchange factors (GEFs) which catalyze the exchange of GDP for GTP, turning the GTPase into the active state; (iii) GTPase activating proteins (GAPs), which promote efficient GTP hydrolysis resulting in an inactive state; (iv) GDP dissociation inhibitors (GDIs), which extracts GDP-Rab from the membrane; (v) GDI displacement factors (GDFs), which assist re-targeting and re-insertion of Rab into the appropriate membrane (Stenmark 2009; Hutagalung and Novick, 2011; Chua and Tang 2015).

Rab31 interacting proteins

- GEFs.

Activation of Rab31 is mediated by several GEFs. Interaction of Rab31 with the different GEFs is mediated by the so-called Vps9 domain (Carney et al. 2006).

Using pull-down assays, Lodhi et al. (2007) demonstrated that Gapex-5 (alternative name: GAPVD1, GTPase activating protein and Vps9 domain 1) directly interacts with Rab31. Another study (Kajiho et al. 2011) found that two members of the RIN family (RIN2, RIN3; Ras and Rab interactor) as well as ALS2 (amyotrophic lateral sclerosis 2) and ALS2CL (ALS2 C-terminal like), but not RIN1 or Rabex-5 (also known as RABGEF1) can act as GEFs for Rab31.

- Cation-dependent mannose-6-phosphate-receptors (CD-M6PRs).

Rab31 is present in small tubulovesicular organelles trafficking from the Golgi/trans-Golgi network (TGN) to endosomes and is involved in the regulation of the formation these vesicles (Rodriguez-Gabin et al. 2001).

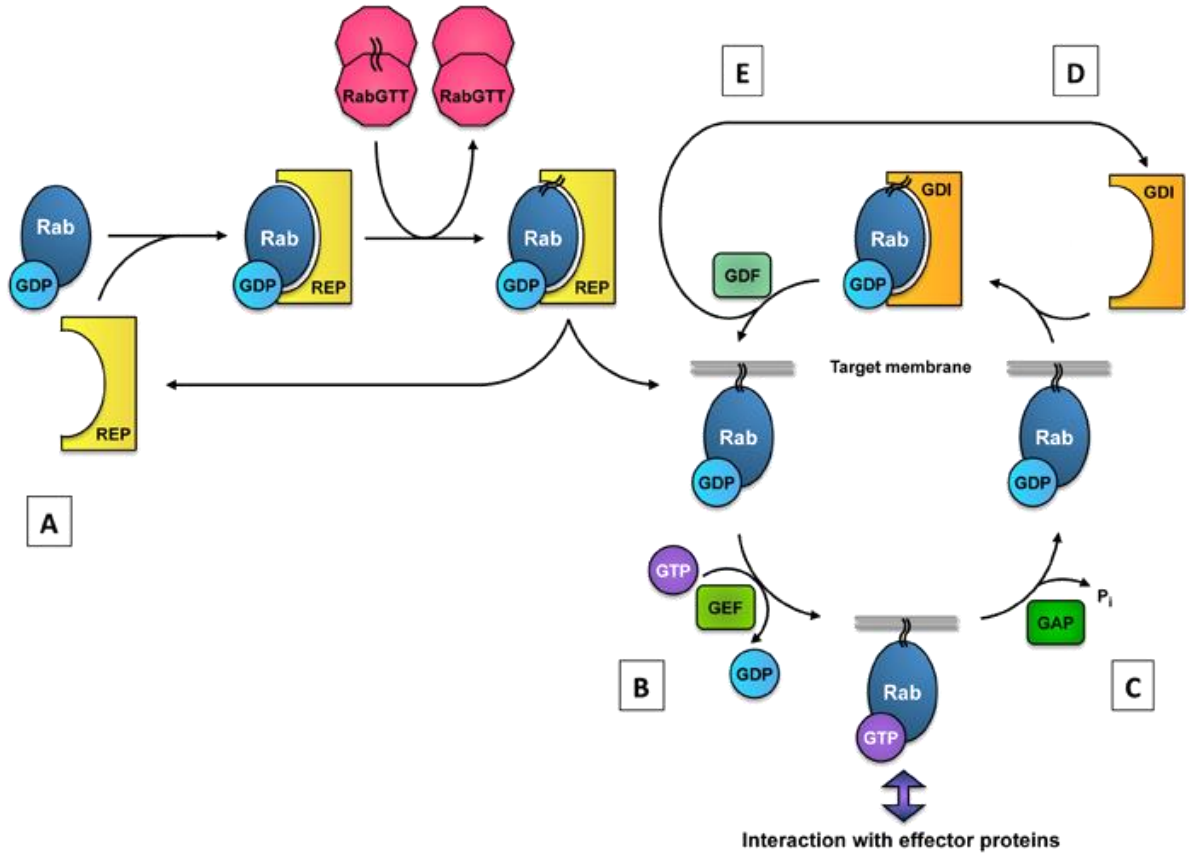


Figure 3. The Rab cycle (A) Newly synthesized Rab proteins are transported by Rab escort proteins (REPs) to geranylgeranyl transferases. **(B)** Guanine exchange factors (GEFs) turn the membrane-associated Rab protein into its active state. **(C)** GTPase activating proteins (GAPs) promote efficient GTP hydrolysis resulting in an inactive state of the Rab protein. **(D)** GDP dissociation inhibitors (GDIs), extract inactive GDP-bound Rab from the membrane. **(E)** GDI displacement factors (GDFs) release the Rab protein from the GDIs and assist re-targeting and re-insertion of the Rab into the appropriate membrane (figure modified from Hutagalung and Novick, 2011).

Besides its role in the Golgi/TGN organization, Rab31 regulates the transport of CD-M6PRs from the TGN to endosomes (Rodriguez-Gabin et al. 2009). Here, RIN3 likely acts as a GEF to regulate Rab31 dependent CD-M6PR-transport (Kajiho et al. 2011). The M6PR system is one of the membrane transport pathways delivering newly synthesized proteins from the TGN to various endocytic compartments. Thus, this transport links biosynthetic to endocytic pathways and, therefore, is majorly involved in the biogenesis of endosomes, lysosomes, and the plasma membrane (Rodriguez-Gabin et al. 2010). Rab31 was also shown to interact with OCRL, a phosphatidylinositol 4,5-diphosphate 5-phosphatase (PI(4,5)P2 5-phosphatase) that regulates the levels of PI(4,5)P2 and PI(4)P, molecules involved in transport and Golgi/TGN organization. Co-localization of Rab31 and OCRL-1 in carriers transporting M6PRs as well as in endosomes may indicate that both proteins are also involved in the targeting and/or fusion of the carriers with endosomes (Rodriguez-Gabin et al. 2010).

- EGF receptor (EGFR).

In addition to its function in the anterograde CD-M6PR-transport, Rab31 plays an important role in the regulation of retrograde EGFR trafficking. Direct interaction of Rab31 with internalized ligand-bound EGFR was demonstrated by co-immunoprecipitation and affinity pull-down assays (Ng et al. 2009). Silencing of Rab31 did not impact internalization of EGFR or its entry in early endosomes, but strongly affected EGFR-transition between early and late endosomes (Chua and Tang 2014). Furthermore, EEA1, a multi-domain tethering factor involved in the fusion of endosomes, also colocalizes with Rab31 suggesting that EEA1 is directly involved in Rab31/EGFR interaction and, by this, is important for Rab31-regulated trafficking of the EGFR between early and late endosomes. Interestingly, silencing of GAPVD1 (Gapex-5), a Rab GEF, reduced Rab31/EGFR interaction and abrogated Rab31-mediated enhancement of EGFR trafficking (Chua and Tang 2014).

- Membrane curvature protein APPL2

Additionally, Rab31, together with other members of the Rab5 subfamily (Rab5a, Rab22a, Rab24, see Fig. 2B), has also been shown to bind the membrane-

curving protein APPL2 (adaptor protein, phosphotyrosine interaction, pleckstrin homology (PH) domain, and leucine zipper-containing protein). APPL2 is associated with a distinct subpopulation of early endosomes that link cell surface signaling and endocytosis (King et al. 2012). In macrophages, Rab31 and its effector APPL2 are largely confined to phagosomal membranes displaying important roles in phagosome closure and FcγR signaling (Yeo et al. 2015)

- Rab31 and glucose uptake.

In adipocytes, insulin-stimulated glucose uptake is mediated by the glucose transporter SLC2A4 (GLUT4). In the absence of insulin, Gapex-5 appears to function as a Rab31-GEF maintaining Rab31 in its active state which leads to intracellular retention of GLUT4. Upon insulin stimulation, Gapex-5 in complex with another protein, the membrane curvature protein TRIP10 (CIP4), translocates to the plasma membrane resulting in decreased activity of TGN-associated Rab31. In consequence, GLUT4 is translocated to the plasma membrane, where it enables increased glucose uptake into the cell (Lodhi et al. 2007). Recently, another Rab31-regulating protein, NGFR (the p75 neutrophin receptor ($p75^{NTR}$)), has been identified (Baeza-Raja et al. 2012). Similar to Gapex-5, $p75^{NTR}$ supports retention of GLUT4 in intracellular vesicles, thus decreasing glucose uptake. Whereas Gapex-5 acts as a GEF, $p75^{NTR}$ may function as a GDI displacement factor, which activates Rab31 by displacing it from its GDIs.

Factors regulating Rab expression

mRNA binding protein HuR.

The ubiquitously expressed mRNA binding protein ELAVL1 (HuR) is a member of the Hu/ELAV-family encompassing four members, HuR, ELAVL2 (HuB or HelN1), ELAVL3 (HuC), and ELAVL4 (HuD). It has been proposed to interact with a series of cancer-relevant genes, thereby stabilizing and translationally enhancing its mRNA targets and, furthermore, modulating their transport between the nucleus and the cytoplasm (Cataluce et al. 2010). In fact, overexpression and/or high cytoplasmic HuR levels (representing the functional pool) are associated with poor outcome in several types of cancer including breast cancer (Wang et al 2013, Heinonen et al 2005). In addition, increased cytoplasmic HuR expression was found to be linked to tamoxifen resistance of MCF7 breast cancer cells (Hostetter et al. 2008). Silencing of HuR leads to the downregulation of Rab31 protein in breast epithelial 184B5Me cells. Furthermore, HuR was demonstrated to directly bind to Rab31 mRNA both in 184B5Me and breast cancer MCF7 cells (Heinonen et al. 2011).

Mucin 1 C-terminal subunit (MUC1-C).

MUC1 (Mucin 1), which is overexpressed in most human breast cancers, is a heterodimeric transmembrane glycoprotein, generated by autocleavage of a single polypeptide (Kufe 2009; 2013). The extracellular N-terminal chain, MUC1-N, contains the O-glycosylated tandem repeats, which are typical for mucin family members. MUC1-N is linked to the cell surface via formation of a non-covalent complex with the C-terminal subunit, MUC1-C, comprising a short 58 aa extracellular region, a 28 aa transmembrane domain, and a 72 aa cytoplasmic tail. The cytoplasmic domain of MUC1-C interacts with various receptor tyrosine kinases such as EGFR and ERBB2 (HER2) and, by this, may modulate downstream signaling pathways (Kufe 2009; 2013). MUC1-C has been demonstrated to be internalized by clathrin-mediated endocytosis. Overexpression of mucin 1 in breast cancer is associated with targeting of the cytoplasmic MUC1-C to the nucleus, where it interacts with ESR1 (estrogen receptor α ERα) and stimulates ERα-mediated gene transcription. One of the target genes activated by the ERα/MUC1-C complex is RAB31, the promotor of which contains an ER-responsive element (Jin et al. 2012). Interestingly, Rab31 in turn stimulates upregulation of MUC1-C, likely by attenuating degradation of MUC1-C in lysosomes. In line with these results, Rab31 and MUC1-C are significantly co-expressed in ER-positive tissues of breast cancer patients (Jin et al. 2012). In a more recent study, MUC1-C was reported to block inhibitory effects of tamoxifen on ERα-mediated Rab31 promoter activity in breast cancer cells (Kharbanda et al. 2013).

Homology

Rab31 belongs to the large Rab protein family (66 human members) of the Ras superfamily of small GTPases. The Rabs can be subdivided into six supergroups, with human Rab31 belonging to group II encompassing nine human members: the quadrupled Rabs RAB5A, RAB5B, RAB5C, and RAB17; the duplicated RAB31 and RAB22A; the duplicated RAB24 and RAB20; as well as RAB21 (Klöpper et al. 2012). Rab31 displays 71.1% identity (86.1% similarity) with Rab22A, whereas for the other members of the superfamily the identity ranges from about 35-45% (with similarities between about 70-78%). An alignment of the nine members of the group II superfamily is given in Fig. 2B.

Implicated in

Breast cancer

Disease

Clinical relevance/prognosis. RAB31 is among 11 genes found to be overexpressed in tumor tissue of estrogen receptor (ER)-positive breast cancer patients by microarray analyses (Abba et al. 2005). Furthermore, RAB31 is one of seven genes that were identified to be strongly upregulated in breast cancer

tissue with high expression of the urokinase receptor (uPAR) splice variant uPAR-del4/5. Similar to uPAR-del4/5, high Rab31 mRNA transcript levels were significantly associated with distant metastasis-free survival and overall survival in 280 lymph node-negative breast cancer patients (Kotzsch et al. 2008). Since Rab31 mRNA independently contributed to the base multivariate models it may serve as a novel prognostic marker in breast cancer. Moreover, the independent but additive prognostic relevance of mRNA expression levels of both, uPAR-del4/5 and rab31, in node-negative breast cancer patients might improve prediction of disease recurrence in breast cancer.

	Rab31 expression	
	low	high
Proliferation		↗
Adhesion		↘
Invasion		↘
In vivo lung colonization		↘

Table 1. Characteristics of breast cancer cells expressing low versus high levels of Rab31
Elevated Rab31 levels in breast cancer cells lead in vitro to increased proliferation, but decreased adhesion and invasion and in vivo to a strongly reduced lung colonization capacity.

Oncogenesis

Tumorbiological relation with uPAR. Not only Rab31 mRNA but also PLAUR (uPAR) mRNA is regulated/stabilized by the RNA binding protein HuR both in vitro and in vivo (Heinonen et al. 2011, Tran et al. 2003).

Therefore, the observed elevated uPAR-del4/5 as well as Rab31 expression in metastasizing breast cancer may be due to increased HuR expression in these tumors and points to a possible relationship between Rab31 and the uPA/uPAR system in cancer cells. Another interesting link between uPAR and Rab31 is the fact that uPAR interacts with the cation-independent mannose-6-phosphate receptor, CI-M6PR (Nykjaer et al. 1998, Kreiling et al. 2003). Interaction of uPAR with CI-M6PR was proposed to be involved in the turnover of uPAR by directing the receptor to endosomes for degradation and, thus, to regulate the cell surface concentration of uPAR as well as internalizing uPAR when it interacts with uPA (Nykjaer et al. 1998). Whether the relationship between uPAR and CI-M6PR might relate to the role of Rab31 in cancer is, however, not yet clear. Possibly, due to its regulatory function in intracellular M6PR trafficking, Rab31 may modulate uPAR activity in cell signaling pathways and/or extracellular matrix interactions/degradation.

Cellular localization. Protein expression of Rab31 was shown in breast cancer tissue by immunohistochemistry using highly specific antibodies for Rab31 (Grismayer et al. 2012). A weak to moderate cytoplasmic staining for Rab31 and, occasionally, strong perinuclear and/or nuclear staining of cancer cells was observed, whereas stromal cells were less frequently stained. Using immunocytochemistry, a pronounced perinuclear staining in MDA-MB-231 breast cancer cells overexpressing Rab31 was found, which was similar to other immunocytochemical studies, showing a perinuclear patch of Rab31 in the trans-Golgi region in different cell types (Grismayer et al. 2012, Ng et al. 2007, Ng et al. 2009).

Modulation of tumorbiological-relevant processes. Grismayer et al. (2012) characterized the phenotype of breast cancer cell transfectants with different Rab31 expression levels in vitro. Elevated Rab31 protein levels were associated with enhanced cell proliferation. Interestingly, weak to moderate overexpression of Rab31 in cell lines with no detectable endogenous Rab31 expression was already sufficient to elicit distinct effects on cell proliferation (Grismayer et al. 2012). Inversely, when Rab31 mRNA levels were stably knocked down by short hairpin RNA interference (shRNAi) in breast cancer cells, which express moderate endogenous Rab31 levels, reduction of Rab31 mRNA/protein expression led to lower cell proliferation rates (S. Soelch and V. Magdolen, unpublished). Additionally, increased expression of Rab31 led to reduced adhesion of cells towards extracellular matrix proteins and decreased invasive capacity through Matrigel™ (Grismayer et al. 2012). In contrast to wild-type Rab31, overexpression of a Rab31 mutant unable to insert into the Golgi membrane, due to deletion of the two C-terminal cysteine residues (Rab31-ΔCC), did not affect in vitro proliferation, adhesion, or invasion (S. Soelch and V. Magdolen, unpublished).

In a xenograft mouse model, the number of lung metastases was found to be significantly reduced in those mice which were inoculated into the tail vein with Rab31-overexpressing cells compared to mice injected with vector control cells expressing basal levels of Rab31 (Grismayer et al. 2012). Considering the fact that high levels of Rab31 mRNA in tumor tissue of breast cancer patients are significantly associated with poor prognosis, this finding at first sight is unexpected.

During tumor progression, however, cancer cells typically acquire different malignant phenotypes: (i) in the initial phase, the growth of the primary tumor, a high proliferation rate is observed and angiogenesis takes place; (ii) then, in order to

metastasize, tumor cells switch to an invasive and motile phenotype leaving their site of origin to generate micrometastases; (iii) finally, at the metastatic site, the proliferative phenotype has to be recovered to trigger growth again (Gao et al. 2005). Rab31, depending on its expression level, may thus modulate a switch between a more proliferative vs. invasive phenotype in breast cancer cells (Tab. 1). Interestingly, it was reported that high levels of the mRNA binding protein HuR which binds and stabilizes Rab31 mRNA (see above), on one hand, lead to increased proliferation and altered cell cycle kinetics in breast cancer cells. On the other, HuR overexpression significantly reduced tumor growth in orthotopic mouse models (Gubin et al. 2010), observations, which are in line with the reported effects of Rab31 overexpression in breast cancer cells.

Using microarray analyses, Rab31 overexpression in breast cancer cells was recently shown to modulate expression of other tumor biologically relevant genes, especially genes of the TGF-β superfamily (Soelch and Magdolen, unpublished). Thus, Rab31 may represent a major player in the change of the cell biological phenotype of breast cancer cells by affecting mainly (non-)canonical TGF-β signaling pathways.

Cervical cancer

RAB 31 was identified by microarray analyses among six genes that associate with tumor expression in the cervical cancer HeLa cell line overexpressing the centrosomal transforming acidic coiled coil TACC3 protein (Yim et al. 2009). Furthermore, Rab31 has been shown to play an important role in cervical cancer progression (Pan et al. 2015). Rab31 overexpression promoted cell proliferation in U87 and SiHa cervical cancer cell lines via activation of G1/S checkpoint transitions, and inhibited cell apoptosis. Moreover, Rab31 overexpression improved U87 and SiHa cancer cell migration, and induced the mRNA expression of epithelial-to mesenchymal transition (EMT) biomarkers depending on the ERK1/2 and AKT pathway. Contrariwise, Rab31 knockdown reduced the growth of U87 and SiHa cells in a nude mouse model in vivo.

Ovarian cancer

In a study evaluating the effects of 17β-estradiol (E2) on the transcriptional level of altered genes in the estrogen receptor (ER)-positive BG-1 ovarian cancer cell line by microarray analyses, RAB31 was among five genes that were significantly upregulated upon treatment with E2 (Hwang et al. 2011). In parallel with the microarray results, the mRNA levels of these genes were significantly induced by E2 (Hwang et al. 2011). With regard to its clinical relevance in ovarian cancer, Rab31 mRNA expression has been analyzed in a cohort of 103 advanced ovarian cancer patients, however, no significant association of Rab31 mRNA levels with progression-free and overall survival of ovarian cancer patients was found (Kotzsch et al. 2011).

Liver cancer

Recently, Rab31 was detected by immunohistochemistry in 94 of 96 tumor tissue samples of patients with hepatocellular carcinoma (HCC), and significantly higher Rab31 expression were observed in HCC tissue as compared to the adjacent non-malignant liver tissue (Sui et al. 2015). High immunoexpression of Rab31 was associated with worse prognosis after curative liver resection and was found to be an independent prognostic factor in HCC. Furthermore, the possible role of Rab31 on HCC progression was examined in different HCC cell lines in vitro. Overexpression of Rab31 in the HCC cell line Huh7 enhanced cell growth and inhibited cell apoptosis. Consistently, silencing of Rab31 in HCC cell line MHCC97 increased apoptosis and suppressed cell viability and cell proliferation. These data suggest that Rab31 may promote HCC cell proliferation by suppressing cell apoptosis (Sui et al. 2015).

Glioblastoma

RAB31, among others, has been reported as a gene showing a cohort (race)-dependent association with progression-free survival in glioblastoma (Serão et al. 2011). In a meta-analysis of microarray studies using Bayesian network analysis, aimed at identifying key genes involved in development of astrocytic tumors, RAB31 was identified as one out of ten upregulated genes that were found to be most influential to development of the highest grade of astrocytoma, Glioblastoma multiforme (Kunkle et al. 2013). Differential expression of all ten genes, including RAB31, at once, increased the lifetime risk of developing glioblastoma to 85.9%, demonstrating the value of Rab31 as biomarker in Glioblastoma multiforme. Interestingly, significant levels of Rab31 were found in neural progenitor cells (NPC), which are believed to be the cells of origin of glioblastoma tumor stem cells (Chua et al. 2014). While overexpression of Rab31 enhanced, silencing hindered the differentiation of NPC to astrocytes suggesting an important role of Rab31 in astroglial differentiation (Chua et al. 2014).

Rab31 protein is rather specifically expressed in GFAP-positive mature astrocytes of adult rodent brains, and is localized mainly in the cell body of astrocytes, and not in the astrocytic processes (Ng et al. 2009). Whereas elevated levels of Rab31 promote cell proliferation in breast or liver cancer cells, in the astroglial cell line A431, Rab31 silencing increased cell proliferation rates compared to the vector control, and vice versa, moderate overexpression of

Rab31 led a reduced cell proliferation (Ng et al. 2009). Since Rab31 in A431 cells also plays a role in regulating EGFR trafficking, one may suggest that altering Rab31 levels affect EGFR traffic leading to an influence on cell proliferation (Ng et al. 2009).

Skin diseases

In psoriasis, a complex inflammatory skin disease, gene expression profiling was used to determine the extent to which the genomic psoriasis phenotype, as defined by the differentially expressed genes between lesional and non-lesional skin, was reversed after treatment with the tumor necrosis factor (TNF) blocker etarnecept in responding patients (Suarez-Farinas et al. 2011). Rab31 was found to be increased in psoriasis tissue but did not fully return to the non-lesional levels after treatment. Immunohistochemically, there were many Rab31 positive cells in the papillary dermis of lesional skin, with fewer positive cells in non-lesional skin. Lowest Rab31 immunoexpression was observed in normal skin. In lesional skin, Rab31 was expressed on CD45+ cells, and also some CD11c+ myeloid dendritic cells and few CD163+ macrophages (Suarez-Farinas et al. 2011).

Rebane et al. (2012) analyzed the differential expression profile of apoptosis-related genes in keratinocytes of atopic dermatitis (AD) vs. normal skin, and the upregulation of immune system-related genes in tissue of chronic AD lesions. RAB31 was one of eight differentially expressed genes that were found upregulated in lesional skin tissue of AD patients suggesting the involvement of Rab31, among other new apoptosis- and inflammation-related factors, in the pathogenesis of AD, especially in long-lasting and refractory cases of the disease (Rebane et al. 2012).

Other disease-related findings

Kidney. Liu et al. (2015) used micro RNA (miRNA) microarray analyses for investigation of the molecular mechanisms of kidney aging. Several Rab proteins including Rab1a and Rab31 were targeted by miR-184and miR-150. Both miRNAs were significantly increased in aging glomerular mesangial cells (GMC) vs. young cells, while Rab31 was significantly lower in aging cells. Transfection of miRNAs into young GMCs suppressed the expression of Rab1a and Rab31, transfected cells showed lower autophagy activities and higher levels of cellular oxidative products, leading to the aging of young GMCs. Otherwise, inhibitors promoted autophagy and reduced oxidative damage by upregulation of Rab1a and Rab31 in old GMCs. This suggests a role of Rab31 in miRNA-inhibited autophagy and promotion of GMC aging (Liu et al. 2015).

Cancer-associated fibroblasts. Bozóky et al. (2013) characterized differentially expressed proteins in the stroma of basal cell carcinoma vs. normal skin fibroblasts. Rab31 was found as one from a panel of twelve proteins that were differentially expressed in cancer-associated fibroblasts (CAF) of basal cell carcinoma but not in normal skin fibroblasts. Besides basal cell carcinoma, Rab31-expressing CAFs were found in a relatively high percentage of tumor samples originating from different tumor types such as squamous cell carcinoma, colorectal, breast, and - to lower extent - lung cancer. Rab31 was not expressed in several types of normal fibroblasts or myofibroblast-like cells in normal tissues (breast, bone marrow, kidney) except for subepithelial fibroblasts of small intestine villi (Bozóky et al. 2013).

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