

Gene Section Review

RANBP2 (RAN binding protein 2)

Erica Di Cesare, Patrizia Lavia

Institute of Biology, Molecular Medicine and NanoBiotechnology (IBMN), National Research Council (CNR), c/o La Sapienza University, via degli Apuli 4, 00185 Rome, Italy (ED, PL)

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Abstract

Review on RANBP2, with data on DNA/RNA, on the protein encoded and where the gene is implicated.

Identity

Other names: ADANE, ANE1, NUP358

HGNC (Hugo): RANBP2

Location: 2q12.3

Note

The human RANBP2 gene lies within a recombination "hot spot" genomic region on Chr 2q11-q13 (Krebber et al., 1997) as part of a gene "cluster" that contains the partially duplicated gene RANBP2L1, containing the RANBP2 5' gene portion (Nothwang et al., 1998).

DNA/RNA

Note

RANBP2 is an essential gene and RANBP2-null mice display early embryonic lethality (Aslanukov et al., 2006; Dawlaty et al., 2008). A single RANBP2 hypomorphic allele is, however, sufficient for viability.

Description

The human RANBP2 gene comprises 31 exons and gives rise to one major mRNA encoding the RANBP2 protein, with at least 8 less represented

alternative splicing variants (AceView; NCBI; GeneCards).

Transcription

RANBP2 mRNA transcription is widespread in many though not all tissues (Fauser et al., 2001). In the mouse genome, the *Ranbp2* promoter region lies in a CpG island, typical of "housekeeping" gene promoters and potentially subjected to epigenetic regulation. In silico analysis of the human RANBP2 gene promoter has identified potential binding sites for cell cycle- and cell proliferation-dependent transcription factors, some validated in chromatin immunoprecipitation (ChIP) assays (e.g., c-Fos, AP1 and others) (GeneCards).

Binding sites for tissue-specific factors are also present, and RANBP2 mRNA transcript and protein product are highly expressed in certain tissues and cell types, e.g. neuronal cells (Fauser et al., 2001).

Serial analysis of gene expression (SAGE) depicted aberrant up-regulation of RANBP2 in certain cancers, e.g. multiple myeloma (Felix et al., 2009).

Protein

Note

Biological overview: The RAN-binding protein 2 (RANBP2) or Nucleoporin 358 (NUP358, nucleoporin of 358 kDa) is the largest component of nuclear pore complexes (NPCs). The latter are highly complex structures composed of several orderly assembled proteins, called nucleoporins (NUPs), that represent gateways across the nuclear

envelope (NE) for the exchange of macromolecules between the nucleus and the cytoplasm. This exchange is critical to many essential processes, e.g., DNA replication, DNA repair, DNA damage response, establishment of functional chromatin domains, replication checkpoint, transcriptional and epigenetic regulation of genes and genome function, mitotic entry.

The RANBP2 nucleoporin is specific of higher eukaryotes and has a multimodular structure (Wu et al., 1995; Yokoyama et al., 1995; Wilken et al., 1995).

It is unique among NUPs in that it is endowed with E3-type ligase activity for SUMO (small ubiquitin-related modifier) peptides (Pichler et al., 2002). This will be discussed in more depth below.

RANBP2 operates in two major groups of cellular processes:

- NPC- and NE-dependent processes ensuring nuclear functions in interphase (e.g., nuclear positioning, recruitment of motor proteins at the NE, centrosome anchoring to the NE, import and export of macromolecules in and out of the nucleus, including transcription and regulatory factors governing genome function); and
- cell division events (NE breakdown, centrosome migration, assembly of the mitotic apparatus, chromosome segregation).

In many of these processes, RANBP2 stimulates the conjugation of SUMO peptides (SUMO-1 to -4) to various target proteins at specific intracellular sites: the nuclear rim in interphase, and microtubules (MTs) as well as kinetochores (KTs) in mitosis. SUMO conjugation is emerging as a protein post-translational modification that modulates the localization and interactions of several proteins (reviewed by Lomelí and Vázquez, 2011; Flotho and Melchior, 2013).

The protein-modifying and transport-regulating activities of RANBP2 target specific substrates in many tissues and cell types. As a result, RANBP2 acts as a cell context-dependent pleiotropic protein in a variety of physiological and pathological processes, including tumor suppression, neuroprotection and familial necrotic encephalopathy.

Description

The human RANBP2 protein is composed of 3224 aminoacidic residues, with a molecular weight of 358 KDa, hence its name (Wu et al., 1995; Yokoyama et al., 1995). The alternative name RANBP2 derives from the presence of four RAN-binding domains (RBD), through which it binds the GTPase RAN. RANBP2 contains several more structural domains:

- **An N-terminal leucine-rich region** anchors RANBP2 to the NPC. This region is also implicated

in binding interphase microtubules (MTs) and regulating their dynamics (Joseph and Dasso, 2008). The structure of this region reveals an alpha-helical domain harboring three central tetratricopeptide repeats (TPRs) capable to bind single-stranded RNA in solution and thought to contribute to messenger ribonucleoprotein (mRNP) remodeling at the cytoplasmic face of the NPC (Kassube et al., 2012).

- **Four RAN binding domains** (RBD1-4) (Yokoyama et al., 1995), 46-60% identical to the prototype RAN-binding domain (Pfam) in the first cloned RAN-binding partner, RANBP1 (Bressan et al., 1991; Coutavas et al., 1993).

The RBDs act as coactivators of GTP hydrolysis on RAN with a dual purpose: a) to assist nuclear protein import, by preventing the accumulation of RANGTP at the NPC cytoplasmic side and avoid that RANGTP prematurely dissociates import complexes while traversing the NPC to reach the nucleus (Yaseen and Blobel, 1999a); b) to facilitate the export of nuclear cargos by assisting the dissociation of RANGTP from exportin-cargo complexes (Bernad et al., 2004).

- **Eight zinc-finger motifs** (Cys2-Cys2 type) in the central portion of RANBP2; they provide a binding platform for exportin-1/CRM1 (Singh et al., 1999) and help CRM1 recycling into the nucleus (Bernad et al., 2004). These motifs can also interact with RanGDP (Yaseen and Blobel, 1999a).

- **Phenylalanine-glycine** (FG) and FxFG repeats (the nucleoporin "signature" motif; x is any aminoacid) present on the fibril-like structures projecting from the NPC into the cytoplasm.

These repeats provide multiple binding sites for nuclear transport receptors (karyopherin beta/importin beta and exportin-1/CRM1). The interaction of FG-rich fibrils with transport vectors facilitates their passage across the NPC.

- **A domain endowed with SUMO E3 ligase** activity, the first enzymatic activity identified for RANBP2 (Pichler et al., 2002), residing between RBDs 3 and 4, that regulates sumoylation of target proteins (more detail below).

- **A C-terminal domain** with peptidyl-prolyl isomerase activity, the second enzymatic activity ascribed to RANBP2 (Lin et al., 2013).

- **A cyclophilin A-like domain**, harbouring an active site cavity that facilitates the binding to the HIV-1 capsid proteins during viral infection (Lin et al., 2013).

Thus far, the SUMO E3 ligase domain, two RBDs, the N-terminal TPR domain and the C-terminal domain have been crystallized and structurally characterized (Vetter et al., 1999; Reverter and Lima, 2005; Geyer et al., 2005; Kassube et al., 2012; Lin et al., 2013).

The SUMO E3 ligase activity of RANBP2 and the RANBP2/RANGAP1*SUMO1/Ubc9 (RRSU) complex

In addition to binding RAN, RANBP2 stably associates with the RAN GTPase-activating protein 1 (RANGAP1) (Mahajan et al., 1997; Saitoh et al., 1997; Matunis et al., 1998; Swaminathan et al., 2004) throughout the cell cycle.

The interaction requires SUMO-1 conjugation to RANGAP1 (Matunis et al., 1996; Mahajan et al., 1997) and the presence of the SUMO ubiquitin-like-conjugating Ubc9 enzyme (Zhang et al., 2002; Zhu et al., 2006), an E2 enzyme that transfers SUMO peptides to SUMO chains, analogous to enzymes acting in the ubiquitination cascade.

RANBP2 is possibly the most abundant SUMO E3 ligase in the cell, and as such has a prominent role in SUMO modification of proteins. Most RANBP2-dependent functions are likely mediated by its activity in SUMO conjugation of target proteins.

The RANBP2 SUMO E3 ligase domain lacks homology to other known SUMO or ubiquitin E3 ligases (Pichler et al., 2004). It is characterized by two 50 aminoacid-long internal repeats, IR1 and IR2 (43% identical), separated by a 20 aminoacid-long linker. Both IR1 and IR2 can bind to Ubc9 and catalyze sumoylation of substrates *in vitro*, though IR2 has lower affinity for Ubc9 than IR1 (Pichler et al., 2004; Tatham et al., 2005).

RANBP2 is quantitatively engaged in complexes with sumoylated RANGAP1 and Ubc9. This binding requires RANBP2's IR1 and the SUMO-interaction motif SIM1, as well as Ubc9. Once IR1 and SIM1 are occupied by RanGAP1*SUMO1 and Ubc9, the E3 ligase activity depends on IR2 (Werner et al., 2012).

In that sense, the entire RANBP2/RANGAP1-SUMO complex (called RRSU complex) is viewed as a multisubunit SUMO ligase.

Indeed, RRSU effectively sumoylates the physiological substrate Borealin *in vitro* (Klein et al., 2009), whereas free RANBP2 does not (Werner et al., 2012).

After NPC disassembly at NEB, RANBP2 remains associated with RANGAP1-SUMO1 and Ubc9 (Swaminathan et al., 2004); RRSU associates with the mitotic spindle and a fraction is recruited to KT's after MTs attach to them (Joseph et al., 2002; Joseph et al., 2004).

Localisation

Intracellular localization: In interphase cells, RANBP2 localizes at the cytoplasmic face of the NPCs (Wu et al., 1995; Yokoyama et al., 1995; Wilken et al., 1995; Walther et al., 2002): RANBP2-containing filaments are anchored to the NPC via interaction with a complex of nucleoporins containing Nup214 and Nup88 (Bernad et al., 2004) and project into the cytoplasm.

Joseph et al. (2002 and 2004) first reported that, at the onset of mitosis, when the NE breaks down and NPCs disassemble, RANBP2 localizes to the

microtubules (MTs) of the forming mitotic spindle, with an accumulation at poles; a fraction is recruited to chromosomal KT's when the latter become attached to MTs (Figure 2, bottom row). This localization underlies RANBP2's mitotic functions (see below). In early telophase RANBP2 is recruited back around chromatin of the reforming nuclei as the NE and NPCs reorganize.

Function

RANBP2 in interphase nucleocytoplasmic transport

As anticipated above, RANBP2 localization at cytoplasmic fibrils emanating from the NPC underlies its function in nucleocytoplasmic transport.

- Nuclear protein import

RANBP2 serves as a docking site for import complexes (the latter are of two main types: either composed of importin vectors interacting with proteins marked by a nuclear localization signal, NLS, or composed of transportin bound to ribonucleoproteins marked by the so-called M9 signal sequence, originally described in hnRNPs).

The docking of import complex at RANBP2 cytoplasmic fibrils of the NPC aids the earliest step in nuclear import (Melchior et al., 1995; Delphin et al., 1997; Mahajan et al., 1997; Yaseen and Blobel, 1999b). RANBP2 itself does not directly participate in import, but facilitates it. In RANBP2-depleted HeLa cells, *in vivo* nuclear import by either Importin alpha/beta (Hutten et al., 2008) or transportin (Hutten et al., 2009) still occurs, but at substantially reduced rates.

In a screening for nuclear proteins that accumulate in the cytoplasm upon RANBP2 depletion, Wälde and coworkers (2012) have also identified direct RANBP2 interactors: they found that an N-terminal fragment of RANBP2, harboring the NPC-binding domain, three FG motifs and RBD1, was sufficient to promote protein import, while neither the interaction with RANGAP1 nor the SUMO E3 ligase activity were required (Wälde et al., 2012). This is consistent with functional mapping data from Hamada and coworkers (2011) using various RANBP2-derived regions to complement RANBP2 knockout MEF cells, in which the RANBP2 N-terminal fragment restored import to RANBP2-null cells; the authors demonstrated a crucial role of this domain in aiding the recycling of RAN and importin beta complexes for nuclear import (Hamada et al., 2011).

In summary, RANBP2 aids nuclear import by at least two mechanisms: i) by "capturing" transport receptors through the FG-repeats, it conveys them towards the NPC and reduces the effective concentration of import receptors required for efficient transport, while ii) by interacting with selected cargos in a receptor-independent manner,

through the RANBP2 N-ter domain, it increases the overall efficiency of nuclear import.

Interestingly, RANBP2 is also implicated in the nuclear delivery and integration of certain human viruses, including Herpes simplex (Copeland et al., 2009) and immunodeficiency virus-1 (HIV-1) (Zhang et al., 2010; Ocwieja et al., 2011; Schaller et al., 2011).

- Nuclear export

RANBP2 also plays roles in mRNA export. Poly(A)⁺ mRNA accumulates in nuclei of RANBP2-null MEFs (Hamada et al., 2011), although the intracellular distribution of poly(A)⁺ mRNA is not affected in RANBP2 hypomorphic mice-derived MEF cells (Dawlaty et al., 2008): thus, mRNA export requires RANBP2, but can proceed, albeit being impaired, in the presence of significantly decreased abundance. These data suggest that RANBP2 facilitates the export pathway, yet is not an indispensable component.

Overall, RANBP2 affects the rate of nucleocytoplasmic transport of many proteins, including transcriptional and epigenetic factors. The latter are often mislocalized in tumor cells and in other cellular contexts in which RANBP2 expression is altered, with a global impact on genome functions. An emerging concept is that tumor cells exploit specific properties of NUPs to deregulate gene transcription, chromatin boundaries and essential transport-dependent regulatory circuits (Xu and Powers, 2009; Köhler and Hurt, 2010).

Structural functions at the nuclear rim and NPCs

RANBP2 has structural roles at the NE besides nuclear transport proper. The development of in situ SUMOylation assays has revealed that both the nuclear rim and PML nuclear bodies are major sites of SUMOylation; RANBP2 inactivation abolished SUMOylation processes along the nuclear rim and reduced the number of PML bodies, while not affecting the nuclear lamina (Saitoh et al., 2006). The loss of nuclear PML bodies has been observed in tumorigenesis, particularly in colon cancer. Satow et al. (2012) reported that β -catenin overexpression disrupts PML bodies in colon cancer cell lines and inhibits RANBP2-dependent SUMOylation of specific PML-associated proteins. The data suggest that RANBP2 is required for SUMOylation of proteins associated with the formation of particular subnuclear structures, the loss of which impinges on nuclear functions in cancer cells.

RANBP2 also recruits motor proteins at the NE to regulate NE breakdown at the onset of mitosis. Through its zinc finger domain, RANBP2 binds the COPI coatomer complex, which coats the Golgi vesicles and contributes to membrane remodelling at the Golgi; the RANBP2-derived zinc finger domain alone dominantly interferes with COPI recruitment to the nuclear rim and inhibits NE breakdown (Prunuske et al., 2006). Interestingly, RANBP2 acts

cooperatively with Nup153, the most nuclear of the NUPs, which contains a distinct zinc finger domain, in coordinating NE breakdown.

RANBP2 also binds to BICD2 (homologous to Drosophila Bicaudal D), an adaptor between motor proteins and their cargo, and recruits BICD2 to NPCs in the G2 phase of the cell cycle (Splinter et al., 2010). BICD2 in turn regulates dynein-dynactin motor complexes at NPCs, and thus centrosome tethering to the NE prior to mitotic entry. BIC2 is also required for the antagonistic activity of kinesin-1, which pushes centrosomes apart. The balance between dynein and kinesin-1 opposite activities governs centrosomal positioning, and hence sites where centrosomes will nucleate the spindle MTs to form asters and later spindle poles; RANBP2 recruitment of BICD2 to the NPCs just before NE breakdown represents a most upstream step in this cascade of events.

A specialized version of this process takes place in radial glial progenitors (RGPs), from which neurons, glia, and brain adult stem cells originate. RGP nuclei migrate basally during G1, then apically during G2 via dynein, and eventually divide at the ventricular surface. Hu et al. (2013) discovered that apical nuclear migration requires dynein recruitment at NPCs by two cooperating G2-specific mechanisms: the "RanBP2-BicD2" pathway acts first, and "Nup133-CENP-F" operates sequentially. This work identifies spatially regulated mechanisms, implying that only restricted regions of neurogenic tissues are permissive for mitosis: in this context, RANBP2 is essential for dynein control of apical nuclear migration, nuclear membrane remodelling and centrosome dynamics prior to mitosis.

Cell differentiation-associated functions

The NPC is not a static transport gate and undergoes dynamic remodelling during differentiation. In myogenic differentiation, myoblasts fuse to form syncytial myotubes. By atomic force microscopy, NPCs have been found to undergo structural differences during C2C12 myogenic cell differentiation from myoblasts to myotubes, parallel to an increased amount of RanBP2 at NPCs (Asally et al., 2011). siRNA-mediated depletion of RanBP2 in myoblasts suppresses differentiation to myotubes. Thus, RanBP2 is required for NPC remodelling in myogenesis, suggesting that a re-adaptation of transport mechanisms, and of the gateways through which these take place, is required as myotubes fuse and many nuclei become immersed in a common cytoplasm.

RANBP2 can carry out more specialized functions in a tissue-specific manner. RANBP2 is highly abundantly expressed in the vertebrate retina. Its cyclophilin domain (which led Ferreira et al., (1996) to classify RANBP2 as Type-II cyclophilin), and the RB4 domain, interacts with opsin, a retinal transmembrane protein; the RBD4 and cyclophilin

domains are therefore proposed to act as a functional "supradomain" with a chaperone function for opsin in the retina. Along with this chaperone function, RANBP2 associates through its cyclophilin-like domain with subunits of the 19S regulatory complex of the 26S proteasome in the neuroretina (Ferreira et al., 1998), and thus contributes to control the stability of proteins that it "chaperones" in the retina. Related to RANBP2 transport functions but independent from them, Cai et al., (2001) identified a novel domain between RBD2 and RBD3 capable of direct association with two MT-based kinesin motors, KIF5B and KIF5C, in neuronal cells. Preventing the interaction of the RANBP2 kinesin-binding domain (KBD) with KIF5B / KIF5C in neuronal cells caused perinuclear clustering of mitochondria, deficits in mitochondrial membrane potential and cell shrinkage (Cho et al., 2007): thus RANBP2 modulates kinesin-dependent mitochondria transport and function. The RBD2, KBD and RBD3 domains of RANBP2 are proposed to constitute a tripartite domain (R2KR3), modulating mitochondrial transport via kinesin subtypes in subsets of neuroretinal cells (Patil et al., 2013). Aslanukov et al. (2006) discovered yet another association of RANBP2, via its leucine-rich domain, with Cox11, a mitochondrial metallochaperone, and HKI (hexokinase type I), defined as the "pacemaker" of glycolysis. Cox11 inhibits HKI activity, but RANBP2 suppresses this inhibition. Consequently, RANBP2 haploinsufficient mice show markedly decreased HKI and ATP levels in the central nervous system, with deficits in growth rates and glucose catabolism (Aslanukov et al., 2006). These mice also show absent or severely reduced cell death response to light-induced oxidative stress in the retina (Cho et al., 2010). RANBP2 cell type-conditional mice models, selectively lacking RANBP2 either in rod or in cone photoreceptors (Cho et al., 2013), showed that RANBP2 ablation in cone photoreceptors promoted their non-apoptotic death, while rod photoreceptors underwent cone-dependent non-autonomous apoptosis. Thus, RANBP2 modulates cell type-specific and distinct pathways of cell death - a key feature of neurodegenerative diseases.

Mitosis

- Mitotic spindle organization

Chromosome segregation at mitosis is crucial to the maintenance of genomic stability, a process often disrupted in cancer. A role of RANBP2 in chromosome segregation was first suggested by the finding that RANBP2 accumulates at the mitotic spindle in prometaphase, and in part at KT's upon MT attachment (Joseph et al., 2002; see figure 2); at these sites RANBP2 remains associated in complex with RANGAP1-SUMO1, suggesting that some of its functions entail RANGTP hydrolysis at specific mitotic sites.

In RNAi-based studies in human cells, RANBP2 down-regulation caused multipolar spindles, with supernumerary poles lacking centrioles (hence suggestive of MT dysfunction) as well as defects in chromosome congression and segregation (Salina et al., 2003; Joseph et al., 2004; Klein et al., 2009; Hashizume et al., 2013). Consistent findings in *Caenorhabditis elegans* embryos (Askjaer et al., 2002) suggest that mitotic functions of RANBP2 are conserved across species in which this protein is present.

- Mitotic microtubule-kinetochore interactions

Further studies showed that RANBP2 depletion resulted in aberrant KT morphology, associated with mis-localization of RANGAP1 and other KT proteins, e.g. Mad1, Mad2, Zw10, Mis12, CENP-A, CENP-E, CENP-F and dynein; RANBP2 depletion also caused lengthened prometaphase duration and chromosome misalignment at metaphase, but the simultaneous depletion of RANBP2 and either Mad1 (Salina et al., 2003) or Mad2 (Joseph et al., 2004), two major spindle assembly checkpoint (SAC) regulators, restored normal prometaphase duration; these findings suggest that RANBP2 depletion-dependent abnormalities activate the SAC. Interestingly, RANBP2 depletion yields unstable KT-MT interactions, suggesting that the concentration of RSSU complex at MT-attached KT's contributes to the functional connections between the spindle and chromosomes prior to chromosome segregation (Joseph et al., 2004). In conditions under which RSSU targeting to KT's was prevented, discrete attachments between MT's and KT's were not maintained, yielding high rates of chromosome mis-segregation (Salina et al., 2003; Joseph et al., 2004; Arnaoutov et al., 2005). Indeed, RANBP2 hypomorphic mice develop severe aneuploidy (Dawlaty et al., 2008).

RSSU targeting to KT's is highly regulated in human cells and requires i) MT attachment to KT's, and ii) proteins that stabilize MT interaction with KT's, e.g. Hec1/Ndc80 and Nuf2 (Joseph et al., 2004).

There is therefore a functional cross-talk between proteins that regulate MT/KT interactions, and RSSU recruitment to KT's, which in turn reinforces these interactions. Interestingly, CRM1 is required for the RSSU complex recruitment to KT's (Arnaoutov et al., 2005) while importin beta overexpression inhibits it (Roscioli et al., 2012).

However, neither endogenous RANBP2, nor GFP-tagged RANBP2 constructs, localize to KT's in MEFs (Hamada et al., 2011). Some cell cycle checkpoints are not yet fully proficient in embryonic cell cycles and some of their regulatory mechanisms may diverge from those operating in somatic cells.

It is worth noting that cells subjected to extended RANBP2 RNAi for longer times eventually escape the mitotic arrest with defective MT/KT connections, originating multinucleated cells and/or

cytokinesis defects (intracellular bridges) followed by cell death (Salina et al., 2003; Joseph et al., 2004). In terms of cancer prognosis, these data suggest that a very narrow threshold, probably modulated by the genetic background of the cells, defines whether defective RANBP2 expression is pro-tumorigenic (by inducing genetic instability in cells that remain viable) or anti-tumorigenic (by preventing normal cell division altogether and inducing the death of the severely aberrant cell products).

Regulation of the SUMO conjugation pathway in mitosis

MEFs with reduced RANBP2 levels are viable and display no overt nuclear transport abnormalities compared to wild-type, yet develop severe aneuploidy associated with chromosome segregation defects, including anaphase bridges (Dawlaty et al., 2008). Chromatin bridges in anaphase are typical of cells in which DNA decatenation is impaired by mutation or inhibition of topoisomerase II alpha (Topo IIa) (Bhat et al., 1996).

Studies in *S. cerevisiae* (Takahashi et al., 2006), *Xenopus* egg extracts (Azuma et al., 2003) and human cells have shown that Topo IIa is subjected to sumoylation (Azuma et al., 2003; Azuma et al., 2005; Mao et al., 2000). Indeed, Dawlaty and coworkers observed that i) RANBP2 hypomorphic MEFs fail to accumulate Topo IIa at inner centromeres in mitosis, and ii) RANBP2 SUMO E3 ligase activity is required for Topo IIa SUMO conjugation and inner centromere targeting, to enable decatenation of sister centromeres prior to anaphase onset (Dawlaty et al., 2008).

RANBP2 also associates with the chromosomal passenger complex (CPC) during mitosis and stimulates sumoylation of Borealin (Klein et al., 2009); this, however, affects neither CPC assembly nor its localization; RANBP2-dependent Borealin SUMOylation might be required for CPC interaction with an as yet unidentified protein(s) at centromeres (Klein et al., 2009).

RANBP2 in cell viability

As remarked, RANBP2 inactivation causes early embryonic lethality (Aslanukov et al., 2006; Dawlaty et al., 2008). Hamada and coworkers (2011) studied mitotic cell viability using a Cre-mediated RANBP2 conditional knockout approach. The incidence of chromosome missegregation was 100% for RANBP2-null MEFs, yet these cells did not die during faulty mitosis and rarely died during the next 12 hours after mitotic exit, suggesting that the mitotic errors caused RANBP2 knock-out are not the primary cause of cell death (Hamada et al., 2011). Rescue experiments, expressing various RANBP2 portions in a RANBP2-null background, revealed that a short N-terminal fragment corrected transport defects and restored cell viability, suggesting prominent NPC dysfunction, rather than mitotic failure, as the cause of cell death (Hamada et al.,

2011). By contrast, RANBP2 siRNA-silenced HeLa cells underwent prolonged metaphase followed by mitotic catastrophe in live cell imaging (Hashizume et al., 2013); the use of a fluorescently-tagged import reporter demonstrated that, under these conditions, RANBP2-depletion-induced mitotic death is not a side effect of failed nuclear import. The discrepancy between these models remains to be explained.

Homology

RANBP2 is conserved among metazoa but absent in *Saccharomyces cerevisiae*.

Mutations

Note

An autosomal dominant mutation of RANBP2 (1880C-->T, yielding the Thr585Met missense mutation in the leucine-rich domain required for binding to both the NPC and to MTs) has been identified in the familial predisposition to acute necrotizing encephalopathy (ANE), arising in otherwise healthy children after common viral infections, such as influenza (Neilson et al., 2009; Loh and Appleton, 2010).

Fusions of the RANBP2 gene with the gene encoding anaplastic lymphoma kinase (ALK) are associated with inflammatory myofibroblastic tumors (see below).

RANBP2 mutants (i.e. point mutations or deletion mutants) have been engineered in several laboratories to study the role of different domains in various cellular processes.

Implicated in

Various cancers

Note

RANBP2 is implicated in many cancer types. It is difficult to draw a single unifying mechanism, yet two recurrent features are worth noting:

a) the SUMO ligase and SUMO-stabilizing activity of RANBP2 targets many mitotic factors, as explained above, which can contribute to genetic instability and tumorigenesis when dysregulated (e.g., RANGAP1 and hence the functional state of RAN at KTs, Topo II, Borealin). Mouse models created by crossing RANBP2 hypomorphic (RANBP2H) and null (RANBP2-) alleles, displaying gradual degrees of RANBP2 insufficiency, are prone to carcinogen-induced and spontaneous tumors: the incidence of skin tumors dramatically increased in mice with reduced compared to wild-type RANBP2 expression and lung adenocarcinomas developed in virtually all insufficient mice (Dawlaty et al., 2008).

b) generally, a striking link exists between some NUPs, their propensity to undergo translocation and fusion with other gene partners and neoplastic diseases (reviewed in Köhler and Hurt, 2010).

RANBP2 shares this tendency with some other NUPs: residing in a chromosomal recombination "hot spot", is involved in several instances of translocation; signalling molecules involved in the resulting fusion protein become aberrantly concentrated at the NE, with tumorigenic consequences (see below).

Inflammatory myofibroblastic tumors

Note

RANBP2 is implicated in a subset of inflammatory myofibroblastic tumors (IMT), rare soft tissue tumors involving mesenchymal cell types, with a prominent inflammatory component. IMTs rarely metastasize, yet often recur rapidly with fatal outcomes in some cases. Some 50% of IMTs harbor rearrangements of the ALK gene (encoding the anaplastic lymphoma kinase ALK), located at 2p23, with diverse partners, and overexpress the ALK protein, mostly in the cytoplasm. In several IMT cases, ALK is fused to RANBP2 and acquires a perinuclear localization. These cases generally have a more aggressive clinical course, suggesting that the RANBP2-dependent ALK perinuclear localization may be prognostic of malignant behavior.

The first two IMT cases with a RANBP2-ALK fusion were described by Ma et al. (2003). By sequence analysis, the N-terminal 867 residues of RANBP2 were fused to the cytoplasmic segment of ALK, originating an 1430-amino acid chimeric protein. In both cases, the RANBP2-ALK fusion was present in myofibroblasts and was nuclear membrane-associated, attributable to the presence of the NPC-binding domain of RANBP2 in the fusion. Patel et al. (2007) reported on an IMT in a young boy (karyotype

45,XY,der(2)inv(2)(p23q12)del(2)(p11.1p11.2),-22) with an ALK-RANBP2 fusion, identified by FISH and confirmed by cloning and sequencing of the breakpoints.

Chen and Lee (2008) described a hepatic IMT with a RANBP2-ALK rearrangement. PCR product sequencing revealed the presence of exon 18 from RANBP2 and exon 20 from ALK. Tumor cells showed a round cell phenotype with nuclear membrane accumulation of ALK protein. Mariño-Enríquez et al. (2011) characterized 11 cases of intra-abdominal IMT with epithelioid morphology. Nine showed perinuclear ALK staining, three of which harbored a RANBP2-ALK fusion. These patients experienced rapid recurrence. The authors suggest that the epithelioid variant of IMT with nuclear membrane or perinuclear ALK represents an aggressive form of sarcoma, with rapid recurrences and frequently fatal. Li et al. (2013) reported two more cases of IMT with RANBP2-ALK fusions, with epithelioid and rounded tumor cell morphology, from the pelvic and peritoneal cavities respectively, both associated with quick recurrence and poor

prognosis. In 2014 the first case of a large tumor appearing in the pleural cavity was described (Kozu et al., 2014) in a patient with massive pleural effusion. The tumor showed the presence of a RANBP2-ALK fusion, rounded cells with an epithelioid shape, and a prominent inflammatory infiltrate, which led the authors to diagnose an epithelioid inflammatory myofibroblastic sarcoma (EIMS) and recognize it as an IMT variant.

An EIMS case arising in the pelvic cavity was also described by Kimbara et al. (2014) as an aggressive variant of IMT.

The tumor cells displayed epithelioid morphology and ALK staining on the nuclear membrane, associated with RANBP2-ALK fusion identified by RT-PCR.

The patient experienced rapid local recurrence after surgery. The tumor was resistant to doxorubicin, but underwent shrinkage after treatment with the ALK inhibitor crizotinib.

Multiple myeloma

Note

Felix et al. (2009) generated SAGE libraries from normal and neoplastic plasma cells to identify differentially expressed genes in multiple myeloma (MM). They identified 46 upregulated genes in the MM library and validated them by qRT-PCR. RANBP2 belongs to a group of upregulated genes in >50% of tested MM cases and in meta-analyses (ONCOMINE database) of MM compared to normal plasma cells. The authors proposed that RANBP2 might be a potential therapeutic target in myeloma.

Acute myelomonocytic leukemia

Note

Maesako et al. (2014) identified a RANBP2-ALK fusion mRNA transcript in a case of myeloid leukemia, associated with the chromosomal inversion inv(2)(p23q13), and resulting in nuclear membrane association of ALK. Another rearrangement involving RANBP2 and ALK was reported by Lim et al. (2014) in an acute myelomonocytic leukemia (AML) in a 31-year-old woman with a karyotype of 45,XX,inv(2)(p23q21),-7[20], associated with a RANBP2-ALK fusion transcript and strong staining of the fusion protein around the nuclear membrane in leukemic cells. The patient had an unfavorable clinical course.

Colorectal cancer

Note

Gylfe et al. (2013) highlighted another type of recombination tumorigenic events involving RANBP2.

Because microsatellite instability occurs in some 15% of all colorectal cancers, the authors sequenced the exomes of 25 colorectal tumors and respective

healthy colon tissue. They confirmed potential mutation hot spots in 15 genes, among which RANBP2; these were validated in tumors with microsatellite instability and showed that RANBP2 also contains hot spot mutations in the validation set.

Proposed tumor-promoting mechanisms of RANBP2 via SUMO-conjugation and stimulation of tumorigenic signaling

Note

The data discussed above indicate some major routes through which RANBP2 can contribute to cancer onset and progression: increasing their genetic instability during mitosis and impairing global nuclear functions in interphase. An increasing implication of SUMO conjugation in the function of proteins relevant to cancer is emerging, particularly in DNA damage and repair.

Among the growing instances of RANBP2-dependent protein SUMOylation, some proteins have established roles in tumorigenic signaling pathways.

Miyauchi et al. (2012) demonstrated a role of RANBP2 in SUMOylation and localization of MDM2, a major regulator of p53 stability, suggesting therefore a possible indirect implication of RANBP2 in p53 functions.

Packham et al. (2014) showed that RANBP2 is implicated in the pro-tumorigenic activity of the insulin-like growth factor-1 receptor (IGF-1R), an activator of the PI3K/Akt pathway with key roles in tumorigenesis.

The biological activity of IGF-1R depends on its nuclear translocation, which in turn depends on SUMOylation. Packham et al. (2014) characterized spatially regulated interactions of IGF-1R, first with dynactin, which transports IGF-1R to NPCs, and therein with importin- β and RANBP2. RANBP2 interacts with and stabilizes sumoylated IGF-1R, enabling its nuclear accumulation and hence the activation of tumorigenic pathways that depend on it. Interestingly, RANBP2 levels are abnormally elevated in transgenic mouse models of prostate cancer constitutively expressing a PI3K catalytic subunit (PIK3CA), and treating the animals with a PI3K inhibitor decreases RANBP2 protein abundance (Renner et al., 2007).

These data converge to suggest functional cross-talks between RANBP2 and tumorigenic pathways.

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