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RINT1 functions as a multitasking protein at the crossroads between genomic stability, ER homeostasis, and autophagy

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ABSTRACT

RINT1 was first identified as an RAD50-interacting protein and its function was therefore linked to the maintenance of genomic stability. It was also shown that RINT1 was a key player in ER-Golgi trafficking as a member of an ER tethering complex interacting with STX18. However, due to early embryonic lethality of *rint1*-null mice, the in vivo functions of RINT1 remained for the most part elusive. We recently described the consequences of *Rint1* inactivation in various neuronal cells of the central nervous system. We observed that lack of RINT1 in vivo triggers genomic instability and ER stress leading to depletion of the neural progenitor pool and neurodegeneration. Surprisingly, we also observed inhibition of autophagy in RINT1-deficient neurons, indicating an involvement of RINT1 in the regulation of neuronal autophagy. Here, we summarize our main RINT1 findings and discuss its putative roles in autophagy.

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It was shown that RINT1 was involved in vitro in ER-Golgi trafficking and in maintenance of genomic stability through its role in G_2/M cell cycle checkpoint and telomere maintenance. More recent studies identify *RINT1* as a tumor suppressor gene and its mutations are associated with predisposition to breast cancer and Lynch syndrome suggesting a putative link between RINT1 and BRCA1, BRCA2 and PALB2 on the one hand, and mismatch repair proteins such as MSH2 and MSH6 on the other hand. These findings put RINT1 at the crossroads of various biological pathways involved in the genome and cell homeostasis (Fig. 1).

To elucidate RINT1s functions in depth, we decided to overcome the early embryonic lethality associated with *Rint1* knockout, by specifically inactivating *Rint1* in the central nervous system (CNS). The CNS is a tissue composed of a great diversity of progenitor and differentiated cell populations which allow us to visualize various types of defects and thereby represents a good tool to dissect the function of a protein. This approach confirmed that at the in vivo level, RINT1 is involved in genomic stability maintenance, ER-Golgi homeostasis and in prevention of ER stress. Interestingly, this work revealed new roles of RINT1 in the regulation of neuronal autophagy and prevention of neurodegeneration.

Before this study, no confirmatory data were available to establish a connection between RINT1 and autophagy. Indeed, RINT1 is shown to interact with UVRAG, a protein essential for ATG9-vesicle formation but this interaction occurs only in the absence of autophagy induction, and RINT1 depletion does not seem to affect ATG9-vesicle formation, minimizing the function of RINT1 in autophagy. Surprisingly, by inactivating *Rint1* in the CNS, we found that RINT1 is essential for the clearance of autophagosomes in neurons in vivo and in vitro. We observed, in fact, in the neurons, an accumulation of SQSTM1/p62, LAMP2 and phospho-RPS6, indicating the impairment of the autophagosomes clearance. The inhibition of autophagosomes' clearance ultimately leads to CASP3-independent neuronal cell death.

Because of this finding, we investigated among all its reported partners and functions, any pieces of evidence linking RINT1 to neuronal autophagy (Fig. 2). We identified several putative pathways/mechanisms that could provide an explanation to the autophagy inhibition in RINT1-deficient neurons. First of all, a well-described cause of late autophagy inhibition in neurons and neurodegeneration, is the disruption of the retrograde transport from distal axons to the stroma of the mature autophagosomes along microtubules mediated by the DYNEIN-DYNACTIN complex. To this point, RINT1 was shown to play a role of ER anchor for the DYNEIN-DYNACTIN -carried vesicles. Therefore, it is conceivable that lack of RINT1 would disrupt autophagosome transport leading to inhibition of autophagy in late stages. Moreover, RINT1 is associated with the STX18 SNARE complex composed among others of STX18 and SEC22B. Interestingly, SEC22B is also reported to belong to the STX5 SNARE complex, which is indirectly involved in autophagosome clearance by assuring the transport of lysosomal proteases from the ER via the Golgi to lysosomes, allowing their proper maturation. Since it was suggested that RINT1 could be involved in ER-Golgi anterograde transport, it could be very likely that RINT1 depletion in neurons would lead

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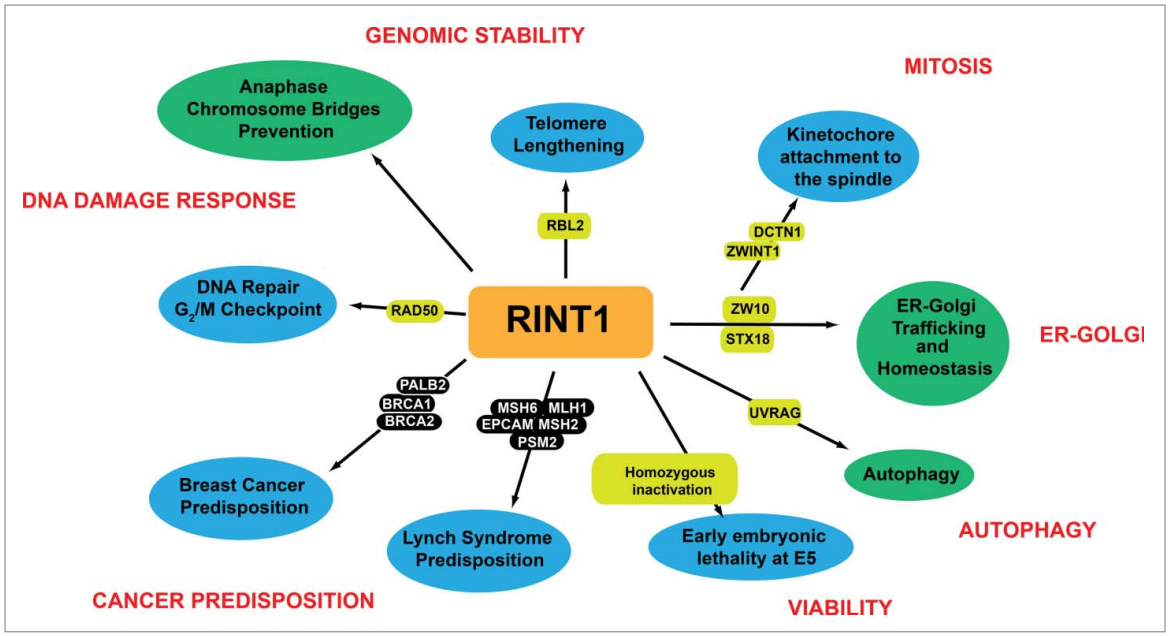

Figure 1. Biological functions of RINT1. Summary of the biological functions of RINT1 in genomic stability, DNA damage response, mitosis, ER-Golgi homeostasis, autophagy and cancer predisposition (in blue, the RINT1 functions described in the literature and in green, the functions highlighted in our manuscript). Identified partners or pathways are identified by stickers in light green. Putative partners and pathways are identified by black stickers.

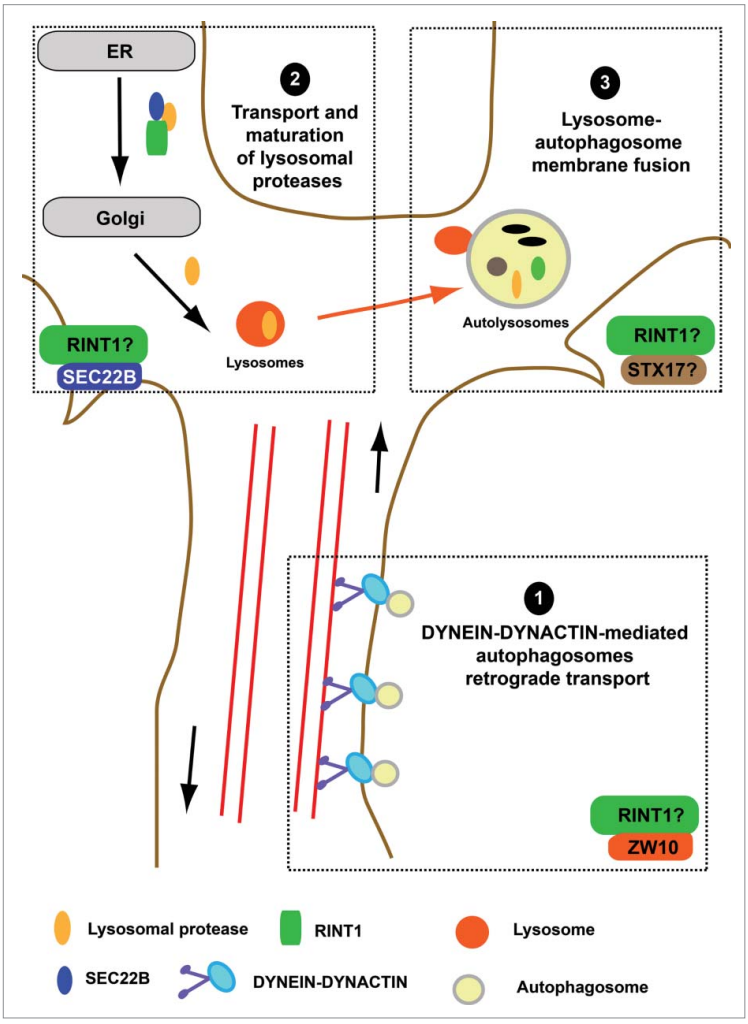

Figure 2. Putative roles of RINT1 in neuronal autophagy. RINT1-deficiency might disrupt the DYNEIN-DYNACTIN dependent-retrograde transport of the autophagosomes in neurons (1). RINT1 could play a role in the transport and maturation of lysosomal proteases such as though interaction with SEC22B (2) or in the membrane fusion of autophagosomes and lysosomes via interaction with the SNARE protein STX17 (3).

to defects in ER-Golgi trafficking and thus would impair the transport and maturation of the lysosomal proteases preventing further proper autophagosome clearance. Finally, it was shown that SNARE proteins such as STX17 are important for the autophagosome-lysosome membrane fusion. Notably, it is reported in the NDEx database (http://www.ndexbio.org), a PtdIns3P interactome study that suggested a STX17 and RINT1 association/interaction. Although these data need to be deepened and confirmed, we could speculate that the lack of RINT1 could interfere with the function of STX17 in autophagosome-lysosome membrane fusion leading to autophagy inhibition.

In conclusion, our study revealed a key role of RINT1 both in development and aging by maintaining genome stability and cell homeostasis and preventing cell death. In addition, it unveiled a novel function of RINT1 in neuronal autophagy. Nonetheless, due to the current lack of data available on RINT1, the exact mechanisms and the RINT1-dependent autophagy tissue-specificity remain to be elucidated.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.