Mini-Review

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Human Mendelian diseases related to abnormalities of the RNA exosome or its cofactors

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Summary **The RNA exosome has a key role in RNA decays and RNA quality control. In 2012, two human Mendelian diseases: syndromic diarrhea/tricho-hepato-enteric syndrome (SD/THE) and Ponto-cerebellar hypoplasia type 1(PCH1) were linked to the RNA exosome or its cofactor's defect. SD/THE's main features are an intractable diarrhea of infancy associated with hair abnormalities, facial dysmorphism, intra uterine growth restriction and immune deficiency. SD/THE is caused by a defect of the SKI complex (*TTC37* and *SKIV2L*), the cytoplasmic co-factor of the RNA exosome for mRNA degradation. PCH1's main features are atrophy of the pons and of the cerebellum, a progressive microcephaly with developmental delay and muscle atrophy secondary to spinal anterior horn cell loss. In 30-40% of patients, PCH1 is caused by a defect in *EXOSC3* which encodes RRP40, a protein of the cap of the RNA exosome. Thanks to knowledge about other forms of PCH it could be assumed that the altered substrates are probably transfer RNA However, as there exists no patient with two null mutations, residual RNA exosome functionality is probably required to preserve viability. Thus, to date two very different human Mendelian diseases have been related to the dysfunctioning of the RNA exosome. It illustrates the versatility of the RNA exosome function and substrate.**

Keywords: Syndromic diarrhea, tricho-hepato-enteric syndrome, RNA exosome, Ponto-cerebellar hypoplasia type 1, *EXOSC3*, *TTC37*, *SKIV2L*

1. Introduction

In 2012, two human Mendelian diseases were linked to the RNA exosome or its cofactor. The RNA exosome, discovered in 1997, has a key role in the RNA decays and RNA quality control (*1,2*). Mostly studied in yeast, it is conserved among eukaryotes and there exist homologs in archea. In yeast, the RNA exosome is a multiprotein complex (Figure 1). The core of the RNA exosome consists of 9 proteins which form a barrel-like structure. Six proteins form the ring of the exosome (Rrp41, Rrp42, Rrp43, Rrp45, Rrp46, Mtr3) on top of which stands the cap of exosome, formed by three proteins (Csl4, Rrp40, Rrp4). Most of the enzymatic activity is brought by associated proteins RRP44 and RRP6 which also have other functions and subcellular localization. Finally two cofactors are needed for RNA exosome function: Mtr4 either alone or with the TRAMP complex (Air1/2, Trf4/5 and Mtr4) and the SKI complex (Ski2, Ski3 and Ski8). The RNA substrates are varied and include messenger RNA, small nuclear RNA, ribosomal RNA, transfer RNA, cryptic unstable transcripts. The RNA decay starts at the 3' end. The human exosome structure is globally the same except for the existence of three paralogs of Rrp44 called DIS3, DIS3L1 and DIS3L2. (*1,2*) (Table 1, Figure 1). Until 2012, only auto immune diseases were linked to the RNA exosome (*3*). Since, two human Mendelian diseases: syndromic diarrhea/ tricho-hepato-enteric syndrome (SD/THE) and Ponto-cerebellar hypoplasia type 1 (PCH1) were linked to the RNA exosome or its cofactor's defect. These diseases emphasize the importance of the RNA exosome in humans but their distinctive phenotypes with few

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overlaps of clinical signs show that an alteration of the function of the RNA exosome can be quite segmentary, probably reflecting the various exosome substrates and functions.

2. Human disease related to the Ski complex

The Syndromic diarrhea/ Tricho hepato enteric (SD/THE) (OMIM : #222466, #614602): SD/THE has been linked to the alteration of *TTC37* and of *SKIV2L*, the orthologs of the yeast's Ski2 and Ski3, two components of the SKI complex (*4-6*). The SKI complex is an obligatory co-factor of the RNA exosome in the cytoplasm in yeast. To date, about 50 patients have been described (*7*). The main clinical features are an intractable diarrhea of infancy requiring parenteral nutrition, facial dysmorphism with a prominent forehead, a broad nose and hair abnormalities (wooly, easily removable), an intra uterine growth restriction, an immune deficiency (lack of immunoglobulin or

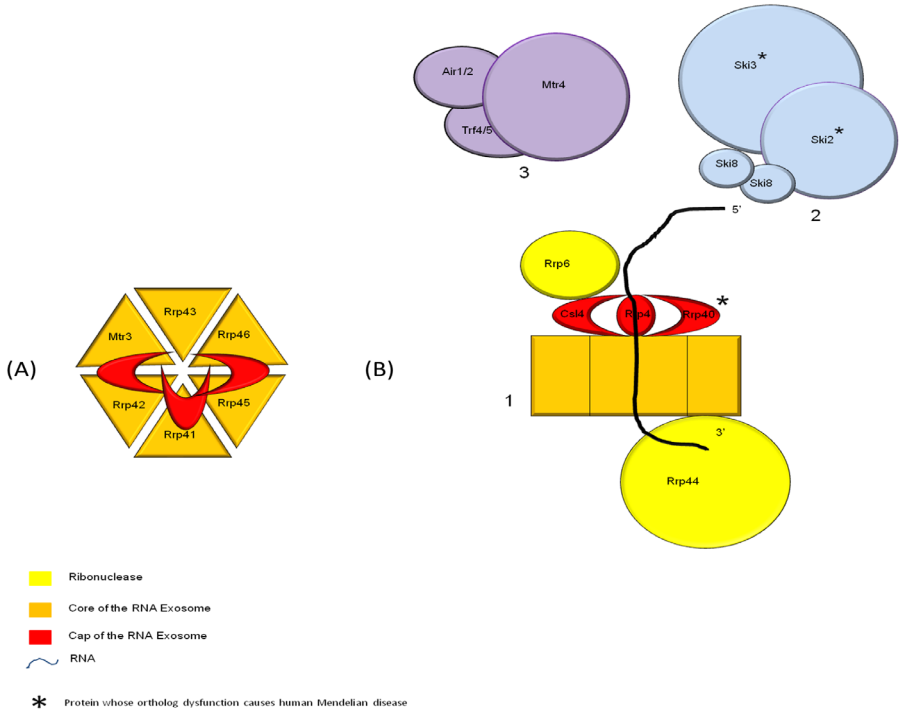

Figure 1. Model of yeast RNA exosome and cofactor. (A), Transversal view of RNA exosome. **(B)**, Front view of RNA exosome (**1**), SKI complex (**2**), and TRAMP complex (**3**).

Table 1. Proteins and genes of the RNA exosome and cofactor in human and yeast

Items	Yeast protein (*S. cerevisiae*)	Human protein	Human gene	Size of the protein (Human, AA)
Cap	Csl4/Ski4	Exosome complex component CSL4	*EXOSC1*	195
	Rrp4	Exosome complex component RRP4	*EXOSC2*	293
	Rrp40	Exosome complex component RRP40	*EXOSC3*	275
Core	Rrp41/Ski6	Exosome complex component RRP41	*EXOSC4*	245
	Rrp46	Exosome complex component RRP46	*EXOSC5*	235
	Mtr3	Exosome complex component MTR3	*EXOSC6*	272
	Rrp42	Exosome complex component RRP42	*EXOSC7*	291
	Rrp43	Exosome complex component RRP43	*EXOSC8*	276
	Rrp45	Exosome complex component RRP45	*EXOSC9*	456
	Rrp6	Exosome component 10	*EXOSC10*	885
	Rrp44/Dis3	Exosome complex exonuclease RRP44	*DIS3*	958
		DIS3-like exonuclease 1	*DIS3L1*	1054
Ski Complex	Ski2	Helicase SKI2W	*SKIV2L*	1246
	Ski3	Tetratricopeptide repeat protein 37	*TTC37*	1564
	Ski8	WD repeat-containing protein 61	*WDR61*	305
Tramp Complex*	Mtr4	Superkiller viralicidic activity 2-like 2	*SKIV2L2*	1042
	Air1	Zinc finger CCHC domain-containing protein 7	*ZCCHC7*	543
	Trf4	PAP-associated domain-containing protein 5	*PAPD5*	572

*The role of the TRAMP complex seems to differ between yeast and human.

absence of vaccine response). In half of the cases, liver abnormalities and skin abnormalities (mostly café au lait spots) are observed. Rarely, a congenital heart defect and platelet abnormalities are associated. The mortality is high with one third of the children deceased before 10 years. About half of the children can be weaned off parenteral nutrition and nearly all have a small size below the 3rd percentile (*8*). The phenotypes resulting from an alteration of either *SKIV2L* or *TTC37* cannot be differentiated, suggesting that it is the absence of the SKI complex which is responsible for the disease. As the SKI complex is linked to a degradation of mRNA in yeast it could be assumed that SD/THE is caused either by the presence of aberrant mRNA or the stabilization of normal transcripts which should be degraded. The clinical management is essentially supportive with nutritional support (mainly parenteral nutrition) and immunoglobulin supplementation.

3. Core RNA Exosome linked human disease

Pontocerebellar hypoplasia type 1 (PCH1) (OMIM #614676): PCH1 has been linked to mutation of *EXOSC3* encoding human RRP40, a protein of the cap of the RNA exosome (*9*). PCH is a group of inherited progressive neurodegenerative disorders with seven subtypes identified to date. All PCH associates atrophy of the pons and of the cerebellum and progressive microcephaly with developmental delay. PCH1 presents the distinctive feature of muscle atrophy secondary to spinal anterior horn cell loss which can lead to hypotonia and respiratory deficiency (*10*). Some patients develop growth retardation (*9*). *EXOSC3* mutations are found in 37% of PCH1 patients (*11*). Patients harbouring mutation in *EXOSC3* differ from other PCH1 patients by a longer lifespan, abnormal oculomotor function, and with time could appear a respiratory deficiency. Nearly 50 patients with a mutation in *EXOSC3* have been described since 2012 (*9,11-13*). Most of the patients present two missense mutations or, more rarely, a compound heterozygosity associating a missense and a null mutation. To date, no patient with homozygous null mutation has been reported. As some level of hypomorphy of the missense mutations exists, it seems that a total lack of RRP40 is not viable. There is some degree of genotype/phenotype correlation: indeed patients with homozygous missense mutation have a milder course, contrary to patients with null mutation and missense mutation. A clinical form with a milder severity has also been described: it associated spasticity, mild intellectual retardation and cerebellar atrophy, and is caused by compound missense mutations (*14*). The clinical management of the patient is symptomatic with nutritional support, and management of dyskinesia, dystonia and seizure (*10*).

4. Discussion

To date, two very different diseases have been related to a defect of the RNA exosome, one concerning the core exosome and the other, one of its co-factors. Except for the short stature found both in SD/THE and in PCH1, there are no shared clinical signs (Table 2). This could be related to an alteration of different types of RNA degradation. Indeed, the RNA exosome is implicated in different RNA degradation pathways: mRNA, Sn RNA, ribosomal RNA, transfer RNA, cryptic unstable transcripts. The ski complex is only necessary for the mRNA degradation (*15*) whereas RRP40 is part of the core of the RNA exosome and is involved in all the RNA exosome functions. Most of the genes causing the other subtypes of PCH are related to the Transfer RNA pathway (*10*). In PCH1, there are no cases of homozygous null mutation and, at least for one mutation, the RNA accumulation typical of exosome knock-out has not been observed (*9*), suggesting that some level of the exosome activity is conserved in PCH1 and that RRP40 is mainly necessary for the transfer RNA degradation, at least in humans. In 2012, the Perlman syndrome, an association of a congenital overgrowth syndrome with tumour susceptibility, was related to *DIS3L2* defect (*16*).

Table 2. Clinical sign Frequency of Syndromic diarrhea/Tricho-hepato-enteric syndrome and Pontocerebellar hypoplasia type 1with mutation in Exosc3

Items	Syndromic diarrhea/Tricho-hepato-enteric syndrome	Pontocerebellar hypoplasia type 1with mutation in *EXOSC3*
Nearly constant (> 90%)	• Intractable diarrhoea • Facial dysmorphism • Hair abnormality • IUGR • Imunodeficiency	• Important developmental delay • Muscle tone abnormal • Pons and/or cerebellar abnormalities
Frequent (50-90%)	• Skin abnormalities • Liver disease • Short stature despite adequate nutrition	• Progressive microcephaly • Respiratory insufficiency • Feeding difficulties
Inconstant (< 50%)	• Congenital cardiac defects • Platelet anomaly	• Epilepsy • Failure to thrive • Short stature • Abnormal oculomotor function

Dis3L2 is an exoribonuclease degrading cytoplasmic mRNA specially uridylated in an exosome-independent pathway (*17,18*). Thus these findings confirm the importance of a controlled homeostasis of RNA product and the potential consequences of imbalance.

In conclusion, to date, two very different human Mendelian diseases have been related to a dysfunction of the RNA exosome. They illustrate the versatility of the RNA exosome function and substrates. The question remains as to whether more diseases human Mendelian could be related to the dysfunction of the RNA exosome. Since non-functional exosome seems not to be viable, only moderate dysfunctions of the RNA exosome or cofactor alterations could be involved.

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