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Review

Yeast and human RNA helicases involved in ribosome biogenesis: Current status and perspectives ☆

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ABSTRACT

Ribosome biogenesis is a fundamental process that is conserved in eukaryotes. Although spectacular progress has been made in understanding mammalian ribosome synthesis in recent years, by far, this process has still been best characterised in the yeast *Saccharomyces cerevisiae*. In yeast, besides the rRNAs, the ribosomal proteins and the 75 small nucleolar RNAs, more than 250 non-ribosomal proteins, generally referred to as *trans*-acting factors, are involved in ribosome biogenesis. These factors include nucleases, RNA modifying enzymes, ATPases, GTPases, kinases and RNA helicases. Altogether, they likely confer speed, accuracy and directionality to the ribosome synthesis process, however, the precise functions for most of them are still largely unknown. This review summarises our current knowledge on eukaryotic RNA helicases involved in ribosome biogenesis, particularly focusing on the most recent advances with respect to the molecular roles of these enzymes and their co-factors in yeast and human cells. This article is part of a Special Issue entitled: The Biology of RNA helicases—Modulation for life.

1. Introduction: general aspects

With the term "RNA helicases", we refer to a group of enzymes or putative enzymes with the capability to catalyse ATP-dependent double-stranded RNA (dsRNA) unwinding and/or hydrolyse ATP in an RNA-dependent manner *in vitro* [1,2]. Perhaps, this term is not the most appropriate to name these enzymes since, as we will discuss later, they are not limited to processively separate long regular dsRNAs as DNA helicases do, but display an array of other biochemical activities including RNA clamping, dsRNA destabilisation, protein displacement from RNA and strand annealing; however, for practical and historical reasons, we have decided to retain the designation "RNA helicases" throughout this review.

RNA helicases have been classified as members of several, up to six, superfamilies of proteins (SF1 to SF6) based on the occurrence and characteristics of various conserved motifs in their primary sequence [3], however, the majority of RNA helicases belong to SF2, which has been further subdivided into several families including the DEAD-box and DExH-box (commonly referred to as the DExD/H-box helicase family) and Ski2 families [1,4]. Among the conserved motifs, all RNA helicases harbour the Walker A and B motifs required for NTP binding and hydrolysis; the additional conserved motifs are required for nucleic acid binding or for coupling NTP hydrolysis to helicase activity [1,4,5]. From structural analyses, it becomes evident that the motifs are a signature for an "RNA helicase core region", which consists of two tandem RecA-like domains connected by a flexible short linker [1]. RNA helicase structures solved in the presence of a bound RNA reveal that the proteins interact with the RNA almost exclusively *via* the sugar phosphate backbone, which explains the lack of nucleotide-sequence specificity of these enzymes. In all cases, the core region is flanked by N- and C-terminal extensions of variable lengths, which often adopt defined folds with specific functions (for examples, see [6–8]). In few cases, it has been reported that these extensions confer physiological specificity or provide complementary catalytic activities to RNA helicases [2,5]. Fig. 1 summarises the characteristic motifs of RNA helicases and the structure of four representative enzymes involved in ribosome biogenesis. In principle, there are no special structural features that allow revealing *a priori* whether or not an RNA helicase is involved in ribosome biogenesis or other RNA metabolic processes.

RNA helicases are ubiquitous in nature as they participate in virtually all aspects of RNA metabolism of living cells. These include transcription, pre-mRNA splicing, RNA editing, small RNA biogenesis and processing, RNA interference, RNA nucleo-cytoplasmic export, ribosome biogenesis, translation initiation and termination, RNA degradation and RNA quality control, organelle gene expression and even viral propagation. Of special importance is the fact that deregulation

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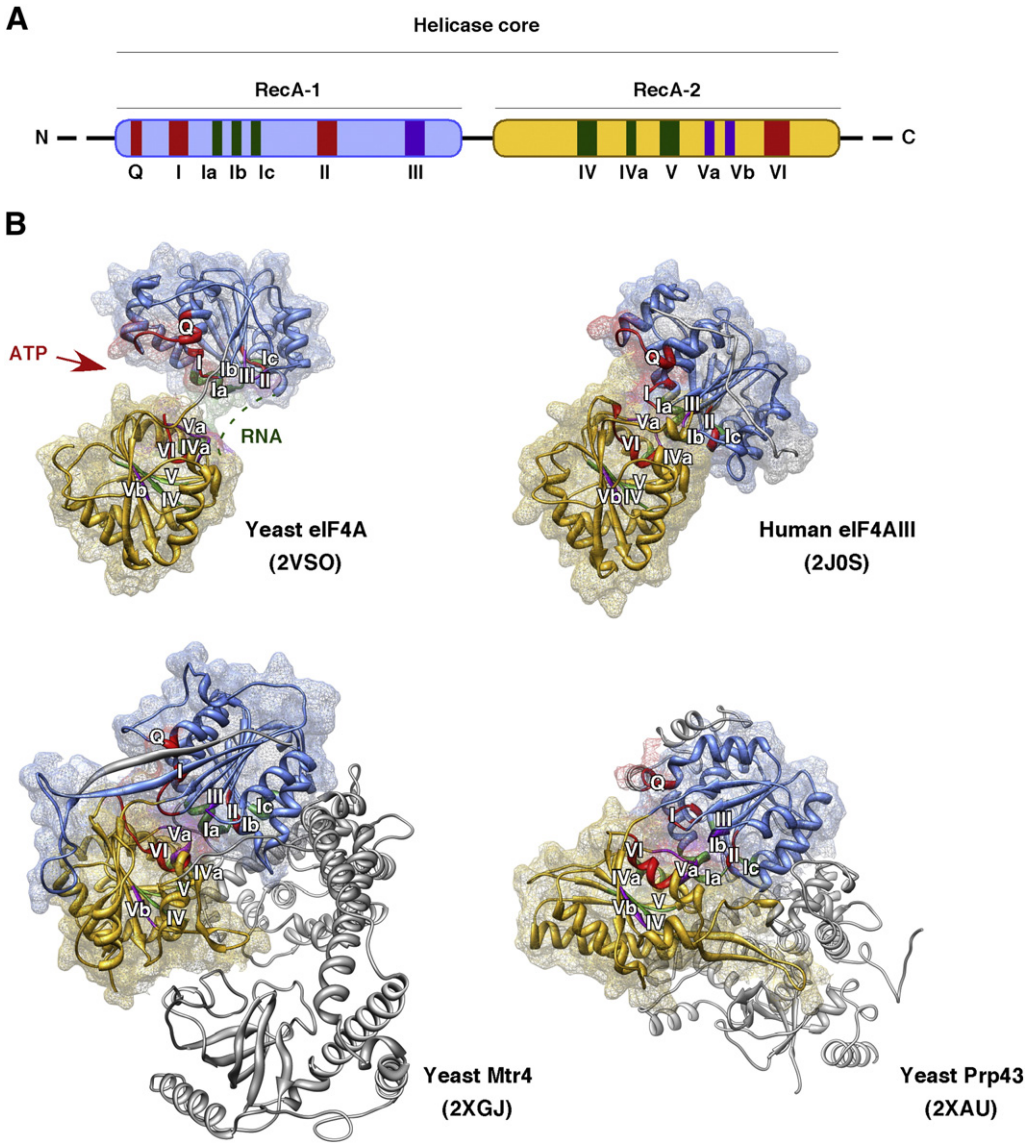

Fig. 1. Structural organization of RNA helicases. (A) The primary sequence of RNA helicases contains a helicase core domain flanked by N-terminal and C-terminal extensions. The helicase core domain consists of two recombinase A (RecA)-like domains named RecA-1 and RecA-2. The core harbours characteristic sequence motifs (boxes) that are shown with different colours according to their predominant biochemical function (red, ATP binding and hydrolysis, green, nucleic acid binding, purple, coordination between nucleic acid and ATP binding). The nomenclature of the characteristic motifs was taken from [1]. The length and the distance between the conserved domains are not drawn to scale. (B) Structure of three RNA helicases involved in ribosome biogenesis (human DDX48/eIF4AIII, yeast Mtr4 and yeast Prp43) and of yeast eIF4A, the prototype RNA helicase of the DEAD-box family. The RecA domains are coloured as in part A and the N- and C-terminal extensions are coloured in grey. The conserved sequence motifs are also coloured as in part A and named. The sequences of these motifs were taken from the alignment of the cores of RNA helicases from different organisms and viruses defined by Jankowsky and co-workers [1]. The positions from where ATP and RNA are bound are also shown. All structures were oriented in a similar manner. The cartoons were generated with the UCSF Chimera program [215], using the atomic model for the crystal structure of the *S. cerevisiae* eIF4A (PDB file 2VSO, [96]), Mtr4 (PDB file 2XGJ, [6]) and Prp43 (PDB file 2XAU, [7]) proteins and human eIF4AIII (PDB file 2J0S, [216]).

of the expression of human RNA helicases contributes to cancer initiation, promotion and/or progression [9].

In this review, we outline the current knowledge about the RNA helicases involved in the biogenesis of cytoplasmic ribosomes of yeast and human cells. Several other reviews on different aspects of RNA helicases have been published in the past few years [1,2,4,5,10–18], including other essays of this special issue. Of particular interest is the recent and instructive review by Bohnsack and co-workers on the function and regulation of RNA helicases during ribosome synthesis [19].

2. Ribosome biogenesis: an overview

Ribosome biogenesis is a complicated multi-step and multi-component process. In all cells, this pathway is strictly controlled to assure the correct composition, structure and function of both ribosomal subunits (r-subunits). Thus, different surveillance mechanisms have evolved to detect, block and/or rapidly degrade excess of ribosomal proteins (r-proteins) and aberrant pre-ribosomal complexes that result from failures in pre-rRNA processing/folding or that lack particular assembly factors or r-proteins (for further discussion, see [20–22]).

In eukaryotes, ribosome biogenesis occurs primarily in the nucleolus, but some events occur in the nucleoplasm, where the pre-ribosomal particles gain export competence, and in the cytoplasm, where the last steps in the maturation of the r-subunits take place (for a review, see [23]). Although ribosome biogenesis is fairly conserved throughout eukaryotes, it has been best characterised in the yeast *Saccharomyces cerevisiae*.