Developmental Biology 437 (2018) 1–16

Contents lists available at ScienceDirect

Developmental Biology

journal homepage: www.elsevier.com/locate/developmentalbiology

Fibrillarin is essential for S-phase progression and neuronal differentiation in zebrafish dorsal midbrain and retina

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ARTICLE INFO

Keywords:
Ribosome biogenesis
Danio rerio
Cell cycle regulation
Optic tectum
Differentiation
Neural progenitors

ABSTRACT

Fibrillarin (Fbl) is a highly conserved protein that plays an essential role in ribosome biogenesis and more particularly in the methylation of ribosomal RNAs and rDNA histones. In cellular models, FBL was shown to play an important role in tumorigenesis and stem cell differentiation. We used the zebrafish as an *in vivo* model to study Fbl function during embryonic development. We show here that the optic tectum and the eye are severely affected by Fbl depletion whereas ventral regions of the brain are less impacted. The morphogenesis defects are associated with impaired neural differentiation and massive apoptosis. Polysome gradient experiments show that *fbl* mutant larvae display defects in ribosome biogenesis and activity. Strikingly, flow cytometry analyses revealed different S-phase profiles between wild-type and mutant cells, suggesting a defect in S-phase progression.

1. Introduction

Fibrillarin (Fbl) is an essential nucleolar protein with a sequence and function conserved throughout evolution (Rodriguez-Corona et al., 2015; Shubina et al., 2016). This protein needs to associate with two other core proteins Nop56 and Nop58 and the RNA-binding protein 15.5-kDa in order to function as methyltransferase. Guided by C/D box small nucleolar RNAs (snoRNAs), fibrillarin catalyzes the 2'-O-methylation (2'-O-Me) of ribosomal RNAs (rRNAs). This post-transcriptional modification is crucial for the precise cleavage and maturation of rRNA, essential for its correct folding and association with ribosomal proteins (Mullineux and Lafontaine, 2012). The 2'-O-Me thus participates to the regulation of ribosome activity. Indeed it has been recently shown that the knockdown of FBL in human cells alters the intrinsic capacity of ribosomes to initiate translation from internal ribosome entry site (IRES) elements (Erales et al., 2017). Finally fibrillarin is also involved in the methylation of histone H2A at rDNA loci, and plays a major role in the regulation of rDNA transcription (Tessarz et al., 2014).

Although ribosome biogenesis is a ubiquitous and fundamental process, fibrillarin expression level was recently shown to vary depending on physiological and pathological contexts (Marcel et al., 2013; Recher et al., 2013; Su et al., 2014; Watanabe-Susaki et al., 2014; Rodriguez-Corona et al., 2015). Previous functional studies on fibrillarin have highlighted its importance in several cellular process. In particular, loss-of-function analyses in yeast and mice have shown that fibrillarin is required for cell survival and early development (Schimmang et al., 1989; Newton et al., 2003). In addition, Watanabe-Susaki et al. showed in cell culture that FBL is important for cell homeostasis and stem cell identity, through the regulation of pluripotency and ability of pluripotent stem cells to differentiate (Watanabe-Susaki et al., 2014). FBL plays a particularly important role in cell cycle regulation, as highlighted by the abnormally high levels of this protein in several cancers, including human breast cancer (Marcel et al., 2013; Su et al., 2014), squamous cell cervical carcinoma (Choi et al., 2007) and prostatic intraepithelial neoplasia (Koh et al.,

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https://doi.org/10.1016/j.ydbio.2018.02.006
Received 5 September 2017; Received in revised form 11 January 2018; Accepted 13 February 2018
Available online 23 February 2018
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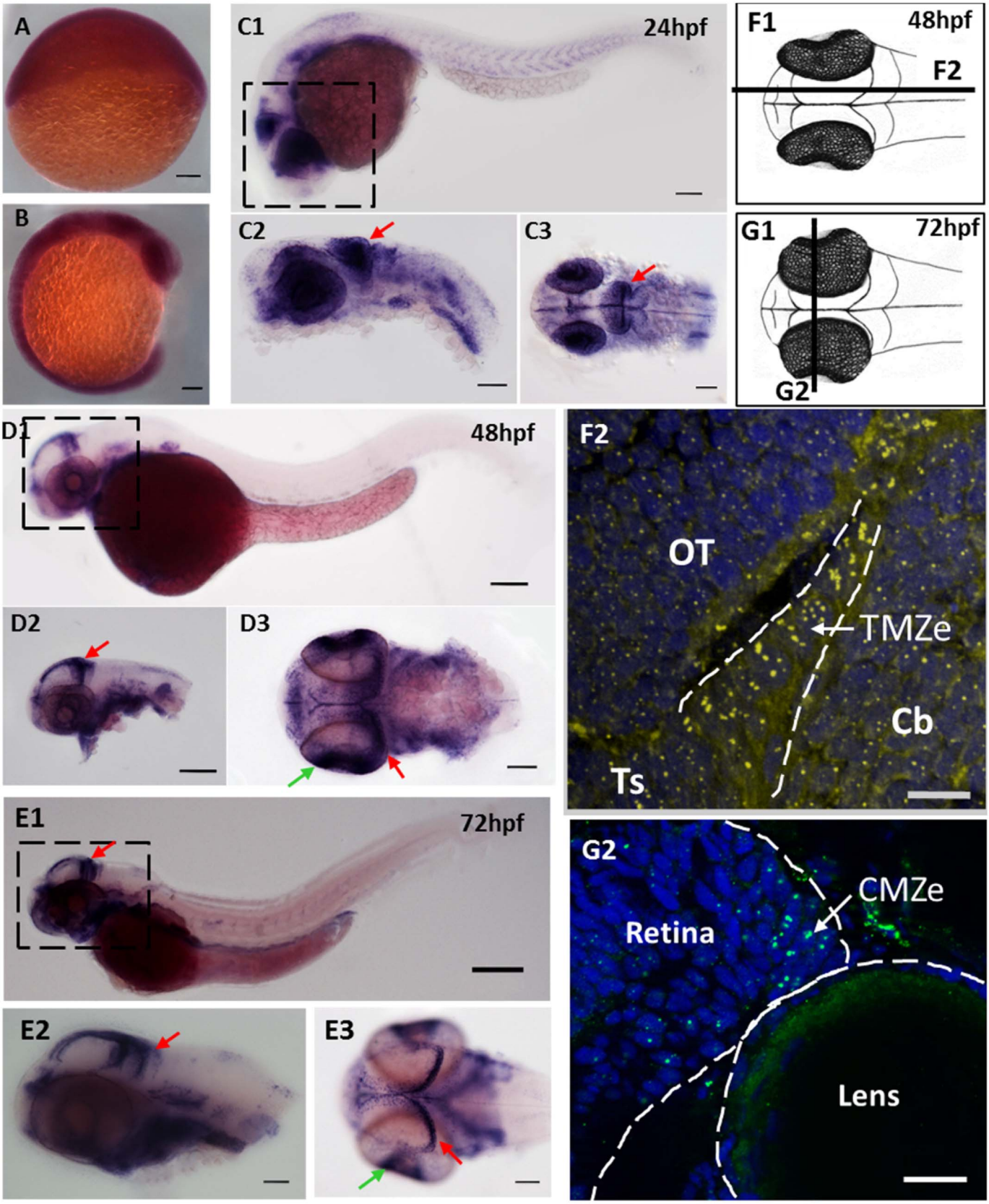
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