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**V. 研究成果の刊行物・別冊
(主なもの)**

Cytoplasmic destruction of p53 by the endoplasmic reticulum-resident ubiquitin ligase 'Synoviolin'

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Synoviolin, also called HRD1, is an E3 ubiquitin ligase and is implicated in endoplasmic reticulum-associated degradation. In mammals, Synoviolin plays crucial roles in various physiological and pathological processes, including embryogenesis and the pathogenesis of arthropathy. However, little is known about the molecular mechanisms of Synoviolin in these actions. To clarify these issues, we analyzed the profile of protein expression in *synoviolin*-null cells. Here, we report that Synoviolin targets tumor suppressor gene p53 for ubiquitination. Synoviolin

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sequestered and metabolized p53 in the cytoplasm and negatively regulated its cellular level and biological functions, including transcription, cell cycle regulation and apoptosis. Furthermore, these p53 regulatory functions of Synoviolin were irrelevant to other E3 ubiquitin ligases for p53, such as MDM2, Pirh2 and Cop1, which form autoregulatory feedback loops. Our results provide novel insights into p53 signaling mediated by Synoviolin.

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Keywords: apoptosis; cell growth; E3 ubiquitin ligase; endoplasmic reticulum-associated degradation; rheumatoid arthritis

Introduction

The ubiquitin–proteasome system (UPS) consists of a small polypeptide ubiquitin, a framework of enzymes that mediates the covalent attachment of ubiquitin to proteolytic substrates and the 26S proteasome that digests the modified proteins into peptides. The formation of ubiquitin conjugates requires the successive action of three classes of enzymes. This process is first activated by an E1 (activating enzyme) in an ATP-dependent manner, forming a high-energy thioester bond between ubiquitin and an E1, and the activated ubiquitin is then transferred to an E2 (conjugating enzyme), forming a similar thioester linkage between ubiquitin and E2, and then E3 ubiquitin ligase transfers ubiquitin to the target proteins. Through repeated reactions of this cycle, a poly-ubiquitin chain is formed on the target proteins, which is recognized by the 26S proteasome for ultimate degradation (Hershko and Ciechanover, 1998; Pickart, 2001). In the UPS pathway, the E3 ubiquitin ligases play critical roles in the selection of target proteins for degradation, because each distinct E3 ubiquitin ligase usually binds a protein substrate with a degree of selectivity for ubiquitination in a temporally and spatially regulated fashion.

Synoviolin, a representative of endoplasmic reticulum (ER)-resident E3 ubiquitin ligases, is a mammalian homolog of Hrd1p/Der3p that “substrates” misfolded carboxypeptidase yscY (CPY*) (Bordallo *et al.*, 1998) and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR), a key enzyme of the mevalonate pathway in yeast (Shearer and Hampton, 2004, 2005). We cloned Synoviolin from rheumatoid synovial cells (RSCs) and described that Synoviolin is highly expressed in synoviocytes of patients with rheumatoid arthritis (RA) (Amano *et al.*, 2003). In that report, we demonstrated that overexpression of Synoviolin in transgenic mice leads to advanced arthropathy caused by reduced apoptosis of synoviocytes. On the other hand, *synoviolin*^{+/-} mice showed resistance to the development of arthritis owing to enhanced

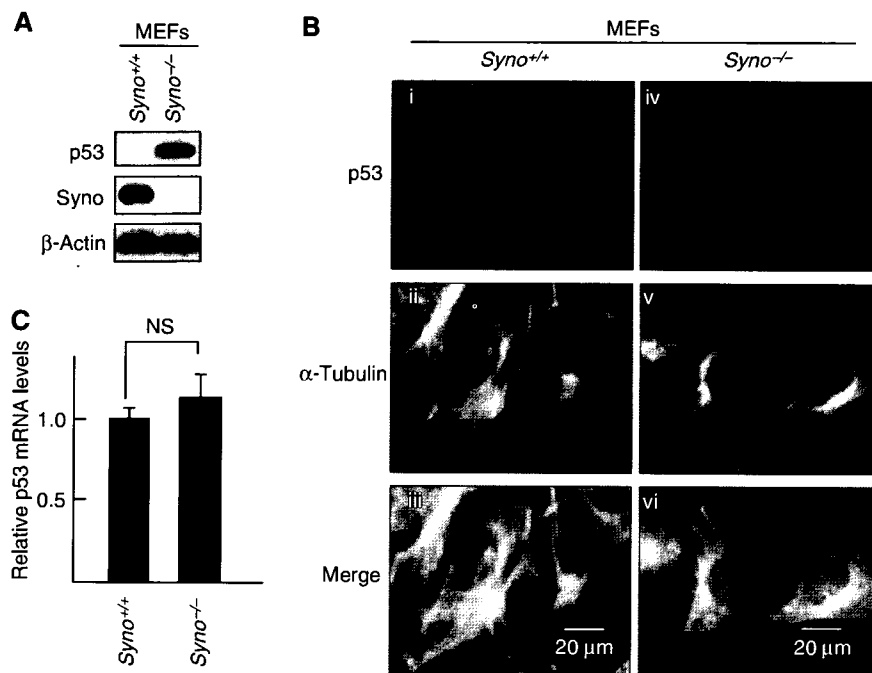


Figure 1 Accumulation of p53 in *synoviolin* null cells. (A) Accumulation of p53 in *Syno*^{-/-} MEFs. (B) Nuclear accumulation of p53 in *Syno*^{-/-} MEFs. p53 in *Syno*^{+/+} MEFs (i–iii) and *Syno*^{-/-} MEFs (iv–vi). Merged images are shown in the bottom panels (iii, vi). (C) Quantification of p53 mRNA. The p53 mRNA level was assessed by real-time PCR and normalized to 18S rRNA. Data are mean ± s.e.m. of four experiments. Statistical analysis using Student *t*-test indicated no significant difference between *Syno*^{+/+} and *Syno*^{-/-} MEFs (NS).

apoptosis of synovial cells. These results indicate that Synoviolin is a novel causative factor for arthropathy based on its anti-apoptotic effects. In another study, we reported that all mice fetuses lacking *synoviolin* (*Syno*^{-/-}) died *in utero* around E13.5 (Yagishita *et al*, 2005), although Hrd1p/Del3p, a yeast ortholog of Synoviolin, was described as non-essential for survival. *Syno*^{-/-} were anemic owing to enhanced apoptosis of fetal liver cells (Yagishita *et al*, 2005). It is surprising that an ER-associated degradation (ERAD)-associated E3 ubiquitin ligase, Synoviolin, is involved in cell hyperplasia of dividing cells via its anti-apoptotic effect. In this regard, like RSCs, the anti-apoptotic effect of Synoviolin was observed even for *synoviolin* expressed ectopically in NIH3T3 cells, which resulted in enhanced cell overgrowth in these cells (Tsuchimochi *et al*, 2005). These results were confirmed also in the *Drosophila* fly (Supplementary Figure 1). An important question remains unanswered at this stage. What is the mechanism of Synoviolin-induced cell overgrowth? The present study was designed to identify the substrates for Synoviolin that may be involved in cell growth.

Results

Accumulation of p53 in *synoviolin*-null cells

To identify target(s) for Synoviolin, we assumed that the lack of Synoviolin results in accumulation of substrate proteins. First, we carried out a two-dimensional polyacrylamide gel electrophoresis (PAGE) using mouse embryonic fibroblasts (MEFs) of *Syno*^{-/-}. In these experiments, p53 was identified as one of the major targets in the profile by LC-MAS analysis (Supplementary Figure 2). Indeed, the level of p53 was markedly enhanced in *Syno*^{-/-} MEFs (Figure 1A) and *Syno*^{-/-} embryos, especially in the posterior part of the body such as somites, brains and maxillary or branchial

arches (Supplementary Figure 3), as reported previously (Gottlieb *et al*, 1997). The accumulated p53 was predominantly localized in the nuclei of *Syno*^{-/-} MEFs (Figure 1B), although the mRNA level of p53 was not altered in *Syno*^{-/-} MEFs (Figure 1C). Phosphorylation of p53 was not observed in *Syno*^{-/-} MEFs (Supplementary Figure 4).

Increment of functional p53 in *synoviolin*-null cells

Next, we tested whether impairment of Synoviolin influences the functions of p53 in the cell. Knockdown of Synoviolin by small interfering RNA (siRNA) for *synoviolin* (*Syno* siRNA) in RKO cells, a human colon cancer cell line known to express wild-type (WT) p53 (Smith *et al*, 1995), resulted in almost complete disappearance of Synoviolin expression (Figure 2A). Synoviolin knockdown was associated with increased p53 protein level and nuclear accumulation of p53 (Figure 2A and B), but no change in p53 mRNA levels (Figure 2C). No changes were noted in the expression levels of other ubiquitin ligases for p53 such as MDM2, Arf-BP (data not shown) and Parc (see Figure 4B), in *synoviolin*-null RKO cells (Brooks and Gu, 2006). On the other hand, the expression levels of unfolded protein response (UPR) markers such as HERP and PERK (Wu and Kaufman, 2006) were increased, which suggests that accumulation of unfolded proteins in *synoviolin*-knockdown RKO cells caused ER stress, followed by UPR (data not shown). These results were confirmed in other cell lines (HEK293 cells and HeLa cells, data not shown). In another experiment, a marked increase was noted in the binding of p53 to its consensus sequences such as *GADD45*, *MDM2* and *p21* promoter in *synoviolin*-knockdown cells compared with *GFP*-knockdown cells (Figure 2D). Furthermore, further additions of the respective competitor abrogated the binding capacity dose-dependently, confirming the specific interactions of p53 on electrophoretic mobility

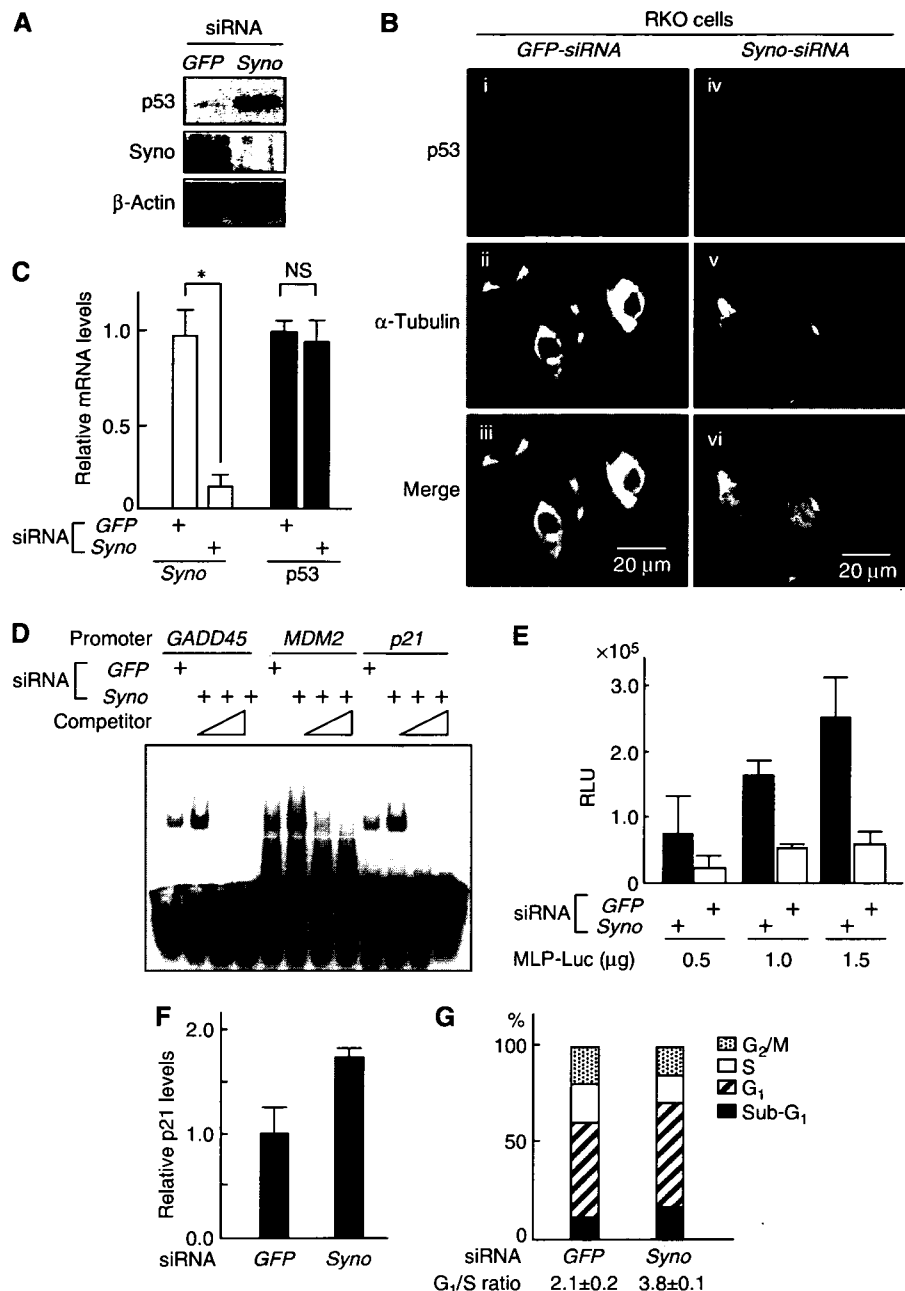


Figure 2 Functional evaluation of increased p53 in *synoviolin*-deficient RKO cells. (A) Increment of endogenous p53 by depletion of *synoviolin*. (B) Depletion of *synoviolin* causes nuclear accumulation of p53. Merged images are shown in the bottom panels (iii, vi). (C) *synoviolin* depletion does not affect mRNA levels of p53. Real-time PCR was performed as in Figure 1C. * $P < 0.01$. (D) DNA-binding activity of p53 for promoters of the indicated genes increases by depletion of *synoviolin*. (E) Transactivation activity of p53 is increased upon depletion of *Synoviolin*. Relative transactivation activity was determined by normalizing luciferase to an internal control, β -Gal activity from RSV- β -gal plasmid. RLU, relative light units. (F) siRNA depletion of *synoviolin* causes activation of p21 expression. (G) siRNA-induced depletion of *synoviolin* induces G₁ arrest. The cell-cycle profile was determined by propidium iodide staining and FACS. The results represent the average of triplicate experiments. Data in (C), (E) and (F) are mean \pm s.e.m. of four experiments.

shift assay (EMSA) (Figure 2D). We also noted three times increment of luciferase activities on *GADD45*-MLP-Luciferase reporter plasmid in *synoviolin*-deficient RKO cells compared with *GFP*-siRNA-treated RKO cells (Figure 2E). Moreover, in *Syno* siRNA-treated RKO cells, we detected enhanced expression of p21, one of the target genes of p53 (Figure 2F), and the accumulation of cells in G₁ phase and decreased cells in S phase (Figure 2G). Taken together, the above results indicate that *Synoviolin* deficiency is not only associated with increased levels of p53, but also with functional activation of p53.

Synoviolin sequesters p53 in the cytoplasm

To understand the molecular mechanism of *Synoviolin*-induced control of p53, we investigated the interaction between *Synoviolin* and p53 *in vitro*. As shown in Figure 3A, GST-Syno Δ TM interacted directly with p53 (lane 8). A series of N-terminus *Synoviolin*-TM deletion mutants showed that the amino-acid sequence 236–270 of *Synoviolin* is responsible for binding with p53 (lanes 1–6) (this binding domain was termed provisionally as '53BD'). Furthermore, a synthetic 53BD peptide inhibited *Synoviolin*-p53 interaction in a dose-