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MDM2/X mediates reduced apoptosis in the plateau zokor: a mechanism of high-altitude adaptation

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Abstract: Murine double minute 2 (MDM2) and murine double minute 4 (MDMX) are critical for the regulation of tumor protein 53 (p53) function and apoptosis. This study compares the *Mdm2/x* gene sequences and functional variations of subterranean zokors from the High Plateau and the Loess Plateau. The findings reveal the molecular mechanisms by which *Mdm2/x* variations drive adaptation to extremely high-altitude conditions—including low oxygen, cold temperatures, and perpetual darkness in underground environments. We cloned and analyzed *Mdm2/x* sequences from two distinct ecological groups of subterranean rodents, *Myospalax baileyi* (plateau zokor) and *Myospalax cansus* (Gansu zokor), and reconstructed phylogenetic trees for a series of subterranean rodents and mammals, as well as the aboveground laboratory rat and humans. We found that MDM2/X in *M. baileyi* and *M. cansus* are involved in the p53-dependent low apoptosis rate, and the variations of phosphorylation sites at the C-terminus of MDM2 contribute to upregulation of p53 transcription and protein expression. We propose that gene evolutionary mechanisms enable survival under these severe combined pressures, and believe that our findings provide critical insight into how genetic modifications drive physiological resilience in Earth's most challenging ecosystems.

Key words: Murine double minute 2/4 (MDM2/X); Plateau zokor; Apoptosis; Adaptation; Extreme environment

1 Introduction

The function of the tumor suppressor tumor protein 53 (p53) is tightly regulated to avoid excessive cell death, which is largely conferred by its target gene murine double minute 2 (*Mdm2*) (HDM2 in humans, chromosome 12q15). MDM2 is an E3 ubiquitin ligase that inhibits p53 through proteasomal degradation, forming a critical negative feedback loop. Its structural homolog, murine double minute 4 (*Mdmx*, chromosome 1q32), also suppresses p53 but lacks ubiquitin ligase activity; instead, MDMX sterically blocks p53's transcriptional activity and stabilizes MDM2 by forming MDM2–MDMX heterodimers to exacerbate p53 degradation (Levine, 2020; Chibaya et al., 2021). In addition to the canonical roles of the MDM2/X–p53 signaling in cancer, dysregulation of this pathway is implicated in chronic pathologies, including inflammation, autoimmune disorders, and neurodegeneration (Brummer and Zeiser, 2024; Efe et al., 2024). Consequently, disruption of MDM2/X with small-molecule inhibitors has emerged as a therapeutic strategy to reactivate p53 (Chandramohan et al., 2024; Wang W et al., 2024).

Survival of the fittest is starkly evident in the high-altitude plateau fauna of China. Facing relentless hypoxia, cold, and solar radiation, species like zokors

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have evolved robust physiological and genetic adaptations through long-term natural selection (Wei et al., 2006; Chen et al., 2007; Zhang ST et al., 2013; Zhao et al., 2013; Zhang T et al., 2022). These extreme-environment species serve as excellent models for decoding adaptive evolution—from whole-organism resilience to adaptive molecular modifications (Liu et al., 2022; Zhang T et al., 2022; Hu et al., 2023; Yu and Zhang, 2023; Zhang XY et al., 2023; An et al., 2024; Wei et al., 2025).

Two subterranean zokor species, *Myospalax baileyi* (synonym *Eospalax baileyi*) and *Myospalax cansus* (synonym *Eospalax cansus*), inhabit distinct high-altitude subterranean environments with divergent selective pressures. *M. baileyi* thrives in the alpine meadow (altitude around 3800 m), characterized by extreme hypoxia, intense solar particle radiation, cold temperatures, and unique geological soil composition (acidity and metal cation content). In contrast, *M. cansus* occupies the Loess Plateau (altitude around 800 m), and is exposed to distinct challenges: high CO_2 levels in burrows and drier soils. These environmental disparities likely drive species-specific physiological and genetic adaptations, particularly in hypoxia response, metabolism, and stress-resistance pathways (Wei et al., 2006; Chen et al., 2007; Deng et al., 2014; Shao et al., 2015; Cai et al., 2018; Gao et al., 2023; An et al., 2024). Previous studies have identified adaptive mechanisms in subterranean species—including *M. baileyi* in China and the blind mole rat in Israel—such as modifications in p53, hypoxia-inducible factors (HIFs), and insulin-like growth factor (IGF) pathways (Chen et al., 2007; Zhang et al., 2013; Zhao et al., 2013, 2016).

In this study, we investigate the transcriptional regulation of MDM2 and MDMX in *M. baileyi* and *M. cansus* in their extreme subterranean habitats. We cloned and analyzed *Mdm2*/*x* sequences from these subterranean rodents and compared them with those of aboveground species. Our findings demonstrate that MDM2/X in *M. baileyi*/*M. cansus* inhibit apoptosis in a p53-dependent manner, with phosphorylation variations at the C-terminus of MDM2 playing a critical role in regulating p53 accumulation. These results reveal how species-specific MDM2/X variants drive adaptation to extreme hypoxic conditions—particularly through suppression of apoptosis. We propose that evolutionary modifications in these genes underlie the remarkable physiological resilience of subterranean rodents, enabling survival under combined stressors, particularly hypoxia.

2 Results

2.1 Comparison and phylogenetic analysis of *M. baileyi* and *M. cansus* MDM2 and MDMX sequences

The *Mdm2* and *Mdmx* messenger RNAs (mRNAs) of the subterranean *M. baileyi* (Tibet Plateau), *M. cansus* (Loess Plateau), and *Rhizomys pruinosus* (bamboo forest) were cloned and sequenced. The coding regions of *M. baileyi*, *M. cansus*, and *R. pruinosus* MDM2 are composed of 1467 bp (coding a protein of 488 aa, KR149455.1), 1464 bp (487 aa, KR149456.1), and 1464 bp (487 aa, PV700090), respectively. The coding regions of *M. baileyi*, *M. cansus*, and *R. pruinosus* MDMX are composed of 1473 bp (490 aa, MH033626), 1473 bp (490 aa, MH033627), and 1476 bp (491 aa, PV700091), respectively. In addition, we also cloned and sequenced *R. pruinosus*-p53 (1164 bp, 388 aa, PV700089) for reconstructing phylogenetic trees.

M. baileyi and *M. cansus* MDM2 proteins have 99.40% identity, and both have identities of 91.00% and 90.40%, 84.80% and 84.20%, 95.70% and 95.00%, 92.60% and 92.60% with human, rat, *Nannospalax galili*, and *R. pruinosus* MDM2 proteins, respectively. *M. baileyi* and *M. cansus* MDMX proteins have 85.70% identity, and both share identities of 82.30% and 84.80% with human, 82.90% and 85.40% with rat, 84.70% and 87.90% with *N. galili*, and 88.90% and 87.80% with *R. pruinosus* MDMX proteins, respectively. Phylogenetic trees based on the MDM2, MDMX, and p53 sequences are similar, indicating that *M. baileyi*, *M. cansus*, *R. pruinosus*, and *N. galili* of subterranean rodents evolved adaptively and convergently under hypoxia and high CO_2 environment (Fig. 1a).

Multiple alignment analysis was performed using Multalin software as described (Corpet, 1988). Both MDM2 and MDMX contain the p53-binding domain, acidic domain, zinc domain, and really interesting new gene (RING) finger domain. The domain sequences of MDM2, MDMX, and p53 are conserved across species (Figs. S1–S3). The variations are widely distributed across the coding regions of *M. baileyi*, *M. cansus*, *R. pruinosus*, and *N. galili*, as well as *Microtus oeconomus* and *Microtus ochrogaster* (Fig. 1b). Some variations occur in the MDM2 coding regions

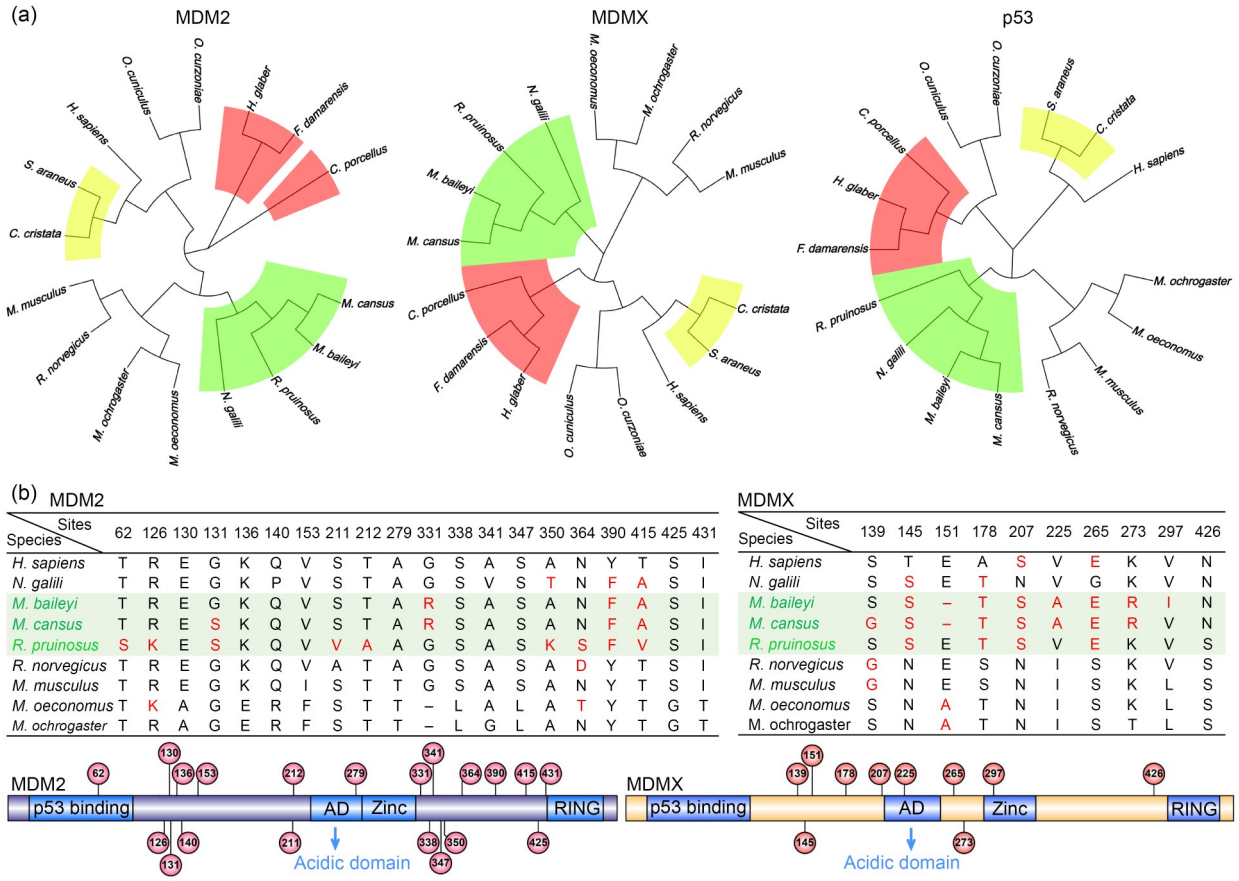
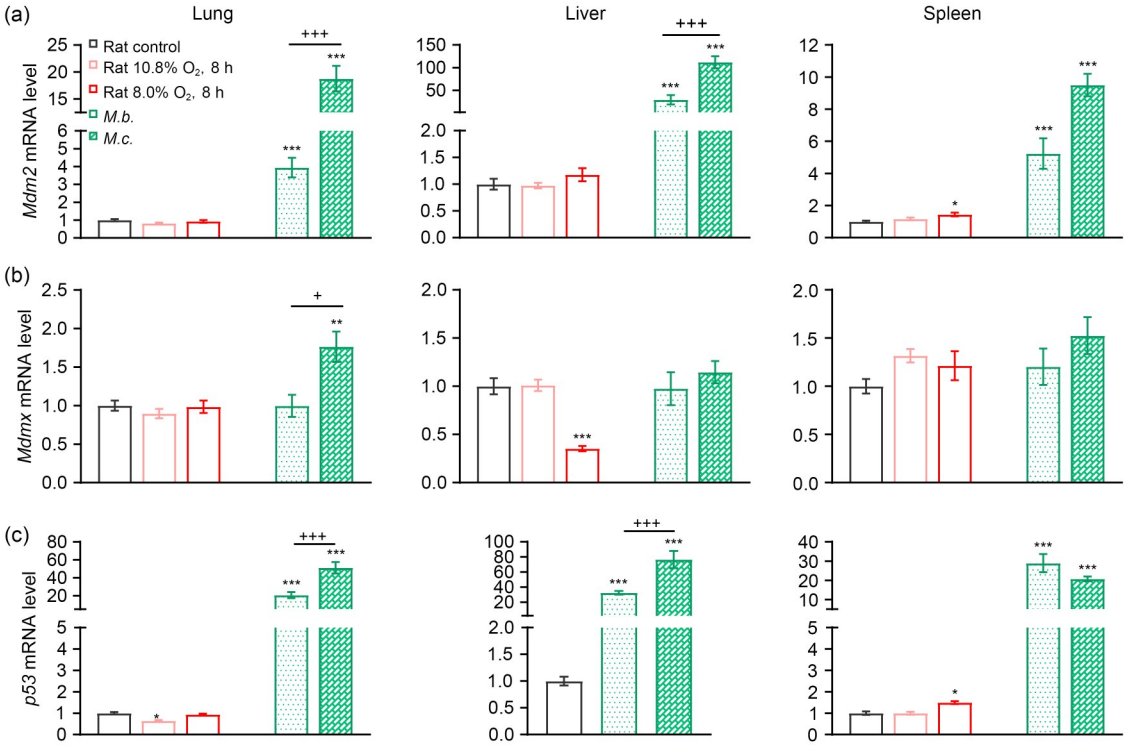


Fig. 1 Comparative analysis of murine double minute 2 (MDM2), murine double minute 4 (MDMX), and tumor protein 53 (p53) gene evolution in subterranean species. (a) Phylogenetic trees based on MDM2, MDMX, and p53 protein sequences of *Myospalax baileyi*, *Myospalax cansus*, and *Rhizomys pruinosus*, as well as those of other subterranean animals, were constructed using the neighbor-joining method (16 species total). Spalacidae in green, Hystricomorpha in red, and Insectivora in yellow. (b) Multiple alignments and variation sites of MDM2, MDMX, and p53 amino acid sequences. The diagrams below show the domain structures of MDM2 and MDMX, along with the corresponding variation codons in *M. baileyi*, *M. cansus*, and *R. pruinosus*.

of *M. baileyi*, *M. cansus*, and *R. pruinosus*, such as T62S of *R. pruinosus* in the p53-binding domain, the unique R126K substitution in *R. pruinosus*, and G131S in *R. pruinosus* and *M. cansus*. There are some variations around the acidic and zinc domains (codons 211, 212, and 331). Interestingly, we found two specific substitutions, T415A/T415V (T in humans and rats) and Y390F (Y in humans and rats), in *M. baileyi*, *M. cansus*, *R. pruinosus*, and *N. galili* between the zinc and RING domains. These sites are involved in the classical ataxia-telangiectasia mutated (ATM)-induced MDM2 activation. There are some variations in the MDMX-coding region, including T145S and A178T in *M. baileyi*, *M. cansus*, and *R. pruinosus*; a codon 151 deletion and V225A in *M. baileyi* and *M. cansus* (near the acidic domain); and the unique K273R substitution of *M. baileyi* and *M. cansus* between the acidic and zinc domains (vs. humans). Thus, MDM2 and MDMX share evolutionarily conserved domains, and the common variations among *M. baileyi*, *M. cansus*, and *R. pruinosus* occur primarily in non-domain regions.

2.2 High *Mdm2* and *p53* mRNA expression in the lung, liver, and spleen of *M. baileyi* and *M. cansus*

We compared the basal transcriptional levels of *Mdm2* and *Mdmx* in different tissues of subterranean zokors and aboveground laboratory rats under hypoxia exposure. Quantitative polymerase chain reaction (qPCR) analysis revealed high expression of *Mdm2* in the lung, liver, and spleen of *M. baileyi* and *M. cansus* (Fig. 2a), while *Mdmx* was notably elevated only in the lung of *M. cansus*. However, hypoxia-exposed lowland laboratory rats showed decreased *Mdmx* mRNA in the



(d)

Tissue	*Mdm2*	*Mdmx*	*p53*	Animal	Stress
Lung	–	–	–	Rat	Control, 20.9% O_2
	–	–	↓		10.8% O_2, 8 h
	–	–	–		8.0% O_2, 8 h
	↑↑↑	–	↑↑↑	*M.b.*	
	↑↑↑	↑↑	↑↑↑	*M.c.*	
Liver	–	–	–	Rat	Control, 20.9% O_2
	–	–	NA		10.8% O_2, 8 h
	–	↓↓↓	NA		8.0% O_2, 8 h
	↑↑↑	–	↑↑↑	*M.b.*	
	↑↑↑	–	↑↑↑	*M.c.*	
Spleen	–	–	–	Rat	Control, 20.9% O_2
	–	–	–		10.8% O_2, 8 h
	↑	–	↑		8.0% O_2, 8 h
	↑↑↑	–	↑↑↑	*M.b.*	
	↑↑↑	–	↑↑↑	*M.c.*	

Fig. 2 Higher levels of murine double minute 2 (*Mdm2*) and tumor protein 53 (*p53*) messenger RNA (mRNA) expression in the lung, liver, and spleen of *Myospalax baileyi* (*M.b.*) and *Myospalax cansus* (*M.c.*). Comparative analysis of *Mdm2* (a), murine double minute 4 (*Mdmx*) (b), and *p53* (c) transcription in *M. baileyi, M. cansus,* and laboratory rats under hypoxia challenge. Values are presented as mean±standard error of the mean (SEM), *n*=6. * *P*<0.05, ** *P*<0.01, *** *P*<0.001 (vs. rat control); $^{+}$ *P*<0.05, $^{+++}$ *P*<0.001 (vs. *M. cansus*). (d) Summarized data for subterranean rodents show significant upregulation compared with laboratory rats under hypoxia. ↑, upregulation; ↓, downregulation; –, unchanged; NA, not available (from published data).

liver and increased *Mdm2* mRNA in the spleen (Fig. 2b). In addition, enhanced *p53* mRNA in *M. baileyi* and *M. cansus* tissues paralleled those of *Mdm2* mRNA (Fig. 2c), whereas hypoxic rats exhibited opposing tissue-specific responses—downregulation in the lung and upregulation in the spleen. These results suggest a unique co-upregulation of *Mdm2* and *p53* in subterranean rodent tissues, distinct from hypoxia-induced expression shifts in rats (Fig. 2d), potentially reflecting adaptive mechanisms to their subterranean environment.

2.3 High MDM2, MDMX, and p53 protein expression in the lung and liver of zokors

As we demonstrated above, the mRNA abundance of *Mdm2*, *Mdmx*, and *p53* in subterranean zokors varies across tissues; therefore, we examined protein

expression. Western blot analysis revealed elevated levels of MDM2, MDMX, and p53 proteins in both lung and liver tissues of *M. baileyi* and *M. cansus* (Figs. 3a and 3b), with high MDMX expression specifically in the spleen of *M. baileyi* (Fig. 3c). In lowland laboratory rats subjected to hypoxia, we observed increased MDM2, MDMX, and p53 protein levels in lung tissue, along with enhanced p53 (but not MDM2 or MDMX) in the liver—a finding consistent with our previous reports (Zhao et al., 2013). Notably, these hypoxia-induced changes were absent in spleen tissue (Fig. 3c). This tissue- and species-specific pattern suggests distinct regulatory mechanisms between constitutively adapted subterranean rodents and acutely hypoxia-challenged rats.

2.4 MDM2/X-induced lower p53-dependent apoptosis in subterranean zokors

To elucidate the regulatory roles of *M. baileyi*- and *M. cansus*-MDM2/X in p53-mediated apoptosis, we conducted gain-of-function experiments in p53-null H1299 cells. Co-expression of rat or *M. cansus*-p53 with their respective MDM2 or MDMX (individually or in combination) significantly enhanced apoptosis (Figs. 4a and 4c), but this p53-induced increase was not observed in *M. baileyi* (Figs. 4b and 4d). Under hypoxia, the apoptosis in subterranean zokor groups was generally lower and was further downregulated by *M. baileyi*-MDM2/X and *M. cansus*-MDM2 (Fig. 4d). A similar phenotype was consistently observed in HEK293T cells. MDM2/X-p53 in *M. baileyi* and *M. cansus* showed lower apoptosis rates under both normoxic and hypoxic conditions (Fig. 4e). These findings demonstrate that *M. baileyi*- and *M. cansus*-MDM2/X exhibit a protective, anti-apoptotic function in p53-mediated apoptosis—functionally independent of cell types—and particularly under hypoxic conditions.

2.5 Increased p53 mRNA and protein expression by *M. baileyi*- and *M. cansus*-MDM2 via C-terminal modifications

To investigate whether the decreased apoptosis in *M. baileyi* and *M. cansus* under hypoxia is related to MDM2/X-mediated regulation of p53 expression,

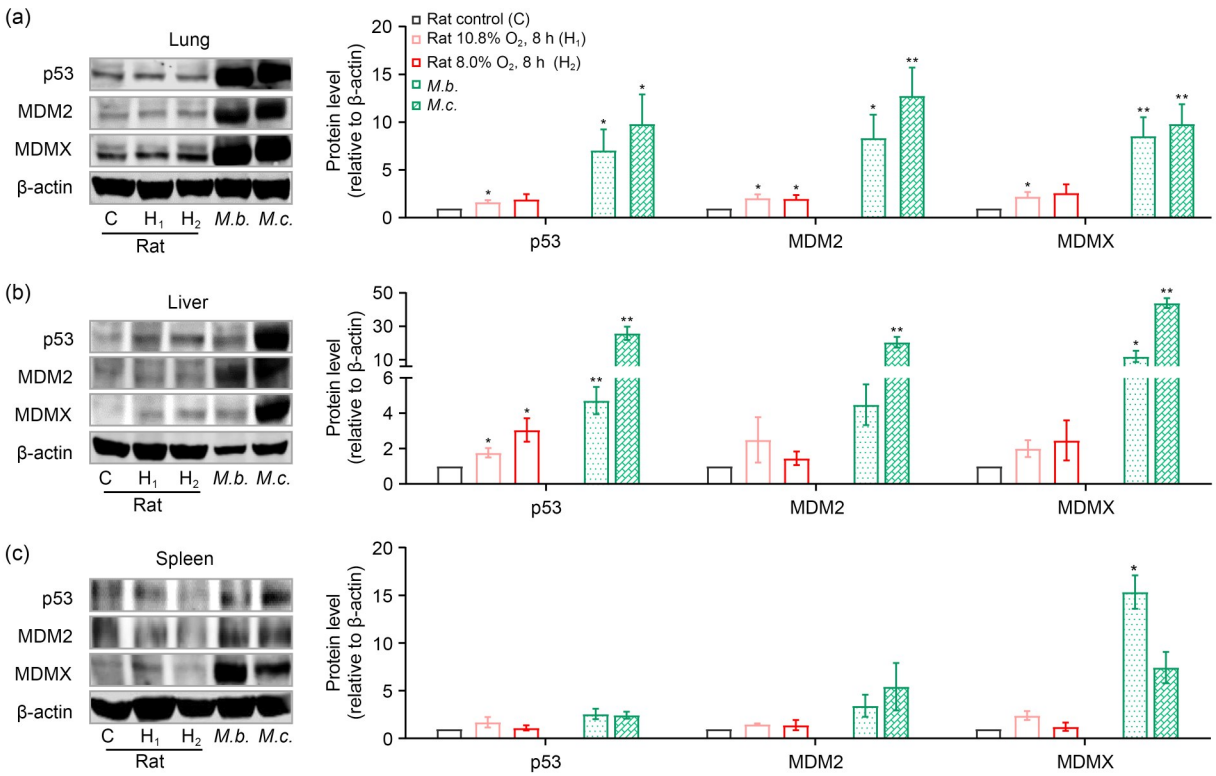


Fig. 3 Protein expression of tumor protein 53 (p53), murine double minute 2 (MDM2), and murine double minute 4 (MDMX) in the lung, liver, and spleen of zokors and rats. Western blotting shows protein expression in the lung (a), liver (b), and spleen (c) in *Myospalax baileyi* (*M.b.*), *Myospalax cansus* (*M.c.*), and laboratory rats under hypoxic stress. Values are presented as mean±standard error of the mean (SEM), n=6. * P<0.05, ** P<0.01 (vs. rat control).

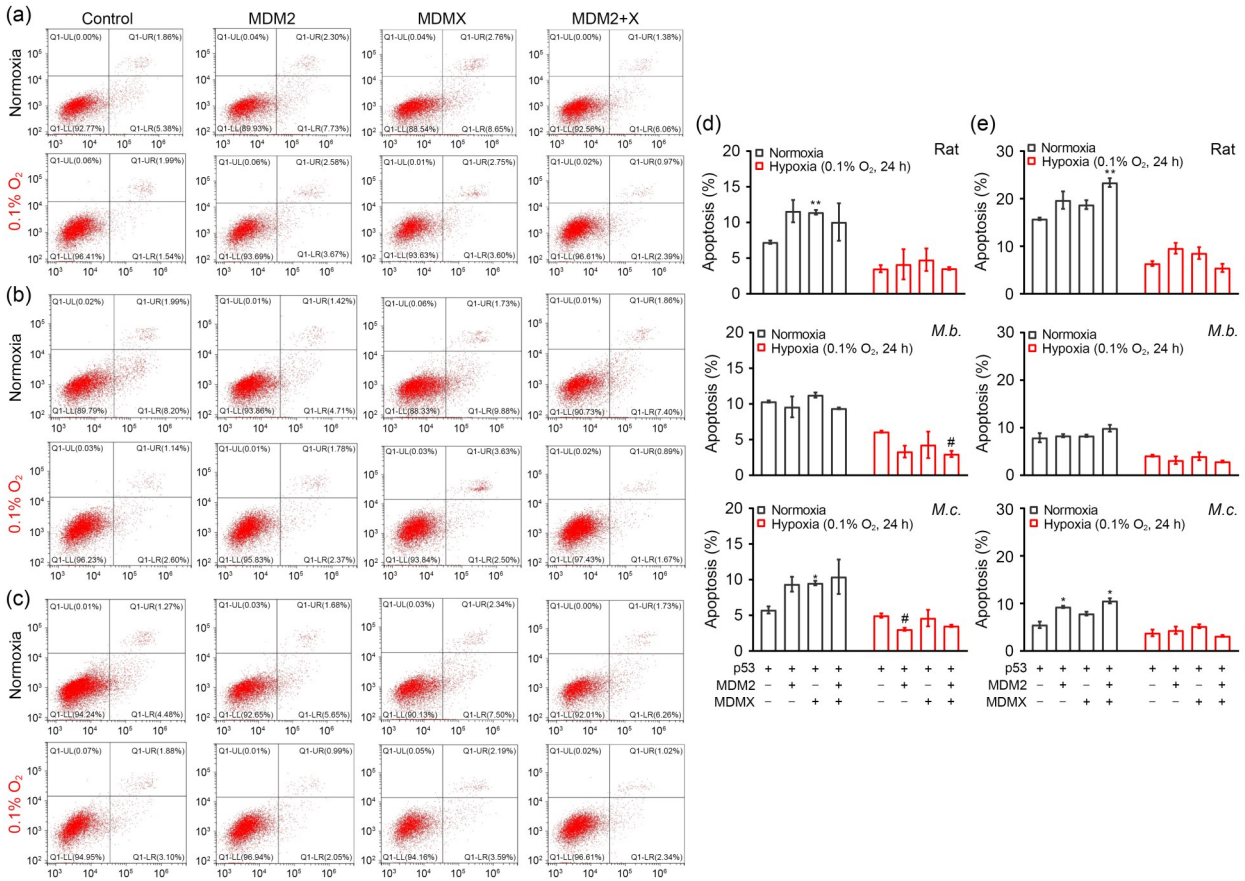


Fig. 4 Effects of murine double minute 2/4 (MDM2/X) on apoptosis in *Myospalax baileyi* and *Myospalax cansus* under normoxic and hypoxic conditions. Apoptosis induced by tumor protein 53 (p53)—co-expressed with MDM2 or MDMX—in laboratory rats (a), *M. baileyi* (*M.b.*) (b), and *M. cansus* (*M.c.*) (c) in the human non-small-cell lung cancer (H1299) cell line was determined by flow cytometry to detect GFP-p53^{+} cells stained with Annexin V-phycoerythrin and 7-amino-actinomycin. Summarized data from H1299 (d) and human embryonic kidney 293 cells (HEK293T) (e) cell lines showed low levels of MDM2/MDMX-mediated, p53-dependent apoptosis in subterranean rodents. Values are presented as mean±standard error of the mean (SEM), n=3. * P<0.05, ** P<0.01 (vs. normoxia trans-p53 only); $^{\#}$ P<0.05 (vs. hypoxia trans-p53 only).

we overexpressed rat-, *M. baileyi*-, and *M. cansus*-p53, MDM2, and MDMX in H1299 cells and measured *p53* mRNA levels. Rat-MDMX and MDM2/X combination significantly decreased the *p53* transcription under hypoxia; however, both *M. baileyi*-, and *M. cansus*-MDM2/X markedly increased *p53* mRNA levels under hypoxia (Fig. 5a). Sequence alignment analysis revealed critical amino acid substitutions in *M. baileyi*/*M. cansus*-MDM2 at two key phosphorylation sites: Y390F (cellular Abelson (c-Abl) tyrosine kinase recognition site) and T415A (ATM serine/threonine kinase recognition site), which are conserved as Y and T in humans and rats, respectively (Fig. 5b). Functional characterization of these variations through site-directed mutagenesis found that wild-type (wt) *M. baileyi*- and *M. cansus*-MDM2 (wt-A415) enhanced *p53* mRNA expression under hypoxia, while the mutant MDM2 (mut-T415, human sequence) abolished this effect. Co-expression of MDM2 with MDMX further potentiated *p53* transcription, whereas mut-MDM2 (T415) with MDMX blocked the enhanced *p53* mRNA expression (Fig. 5c). These findings indicate that the variations of *M. baileyi*/*M. cansus*-MDM2 contribute to the accumulation of *p53* transcription under hypoxia stress via C-terminal loss-of-phosphorylation modifications; however, the co-factor MDMX had little effect. Furthermore, we observed that transfected rat-MDM2 can inhibit p53 protein expression in a dose-dependent manner of MDM2, reversible by Nutlin-3a, an inhibitor of the MDM2-p53 interaction by binding to the binding cleft of MDM2 (Anil et al., 2013). However, overexpressed *M. baileyi*-MDM2-wt (A415, F390) significantly increased p53 protein levels dose-dependently. Notably, reactivating the c-Abl and ATM kinase on

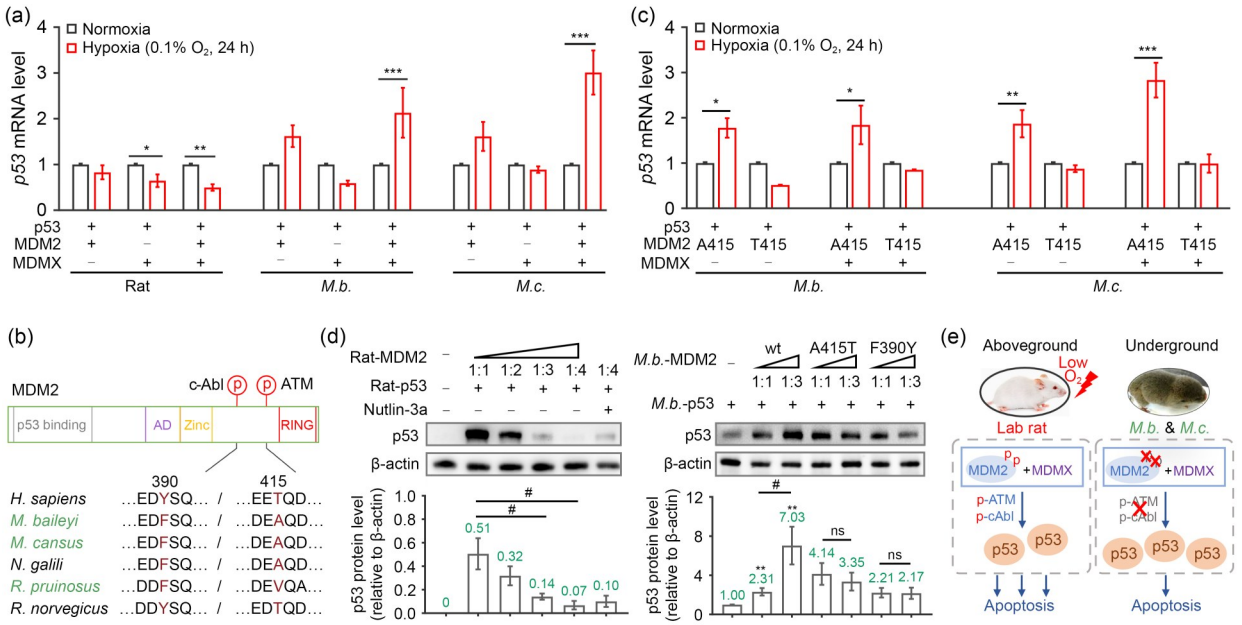


Fig. 5 Effects of *Myospalax baileyi* (*M.b.*)/*Myospalax cansus* (*M.c.*)-murine double minute 2/4 (MDM2/X) on the expression of tumor protein 53 (p53) messenger RNA (mRNA) and protein. (a) MDM2 and MDMX from *M. baileyi*/*M. cansus* increased *p53* mRNA expression under hypoxic stress. Values are presented as mean±standard error of the mean (SEM); n=3; * P<0.05, ** P<0.01, *** P<0.001 (vs. normoxia). (b) Schematic diagram showing the F390 and A415 substitution sites in the C-terminal coding sequences (CDSs) of MDM2. (c) *M. baileyi*/*M. cansus*-mutant MDM2 (A415T) blocked hypoxia-enhanced *p53* mRNA expression in human non-small-cell lung cancer (H1299) cells. Values are presented as mean±SEM; n=3; * P<0.05, ** P<0.01, *** P<0.001 (vs. normoxia). (d) Rat-MDM2 decreased p53 protein levels in a dose-dependent manner, whereas wild-type (wt) *M. baileyi*-MDM2 upregulated p53; however, the A415T and F390Y mutants of *M. baileyi*-MDM2 decreased p53 protein levels in a dose-dependent manner. Values are given as mean±SEM; n=3; * P<0.05, ** P<0.01, ^{ns} not significant, P>0.05 (vs. trans-p53 only); $^{\#}$ P<0.05 (vs. co-trans-p53:MDM2 wt=1:1). (e) In aboveground laboratory rats, the MDM2/MDMX heterodimer is activated under hypoxia, leading to increased p53 via ataxia-telangiectasia mutated (ATM) and cellular Abelson (c-Abl) kinases (phosphorylating MDM2 at T415 and Y390) and resulting in p53-dependent apoptosis. In contrast, in subterranean zokors, loss-of-phosphorylation variants (A415 and F390) inhibit MDM2 activation yet still permit p53 accumulation (at both mRNA and protein levels) with concomitantly low apoptosis. AD: acidic domain; RING: really interesting new gene.

MDM2 phosphorylation of *M. baileyi*, the mut-MDM2 (A415T and F390Y) blocked the elevated p53 protein, depending on MDM2 doses (declining trend) (Fig. 5d), which indicated that wt-MDM2 of *M. baileyi* and *M. cansus* (A415, F390) abolished the MDM2 canonical function on p53 suppression, leading to p53 accumulation both on mRNA and protein levels. In addition, we analyzed the predicted three-dimensional (3D) structures of MDM2, MDM2-p53 complex, MDMX, and p53 proteins in rats, *M. baileyi*, and *M. cansus* (Figs. S4 and S5). The monomer structures of MDM2, MDMX, and p53 are similar in the functional domains of these species (Figs. S4a and S5). However, disordered regions at the MDM2 C-terminus cause the mismatching structures in Rat and *M. baileyi* (Fig. S4b$_1$). The variations of F390 and A415 in *M. baileyi*-MDM2 modified the hydrogen bonds between residues, gaining a hydrogen bond at F390 and losing one at A415 (Figs. S4b$_2$ and S4b$_3$). Overall, the p53 monomer-MDM2 complex structures in rat and *M. baileyi* are highly similar (Fig. S4c). We further analyzed the structures of the p53 dimer-MDM2 complex that initiates p53 degradation via ubiquitination. In the rat-p53 dimer-MDM2, the structures of the C-terminal portion of MDM2 adopt relatively stable helical conformations proximal to rat-p53. In contrast, the C-terminal disordered chains of *M. baileyi*-MDM2 (near the F390 and A415 variations) were observed in the *M. baileyi*-p53 dimer-MDM2 complex, indicating its greater conformational flexibility. These natural MDM2 variation sites abolish the c-Abl/ATM-mediated phosphorylation, which might be beneficial for the adaptation to the underground conditions by sustaining p53 stability and thereby suppressing apoptosis (Fig. 5e).

3 Discussion

3.1 Evolution and diversity of MDM2/X variations

MDMs are involved in adaptations to stress and precise control over the tumor suppressor p53. Vertebrates carry both paralogues, MDM2 and MDMX (Tan et al., 2017). We found evolutionary conservation of MDM2/X in both subterranean and aboveground species (Fig. 1a), including Spalacidae (*M. baileyi*, *M. cansus*, *N. galili*, and *R. pruinosus*), Hystricomorpha (naked mole rat, Damaraland mole rat, and guinea pig), and Insectivora (star-nosed mole and shrew), indicating that the MDM family shares a common ancestral gene; the duplication event likely occurred early in vertebrate evolution. Both MDM2 and MDMX possess p53-binding, acidic, zinc finger, and RING domains—conserved throughout evolution (Figs. S1 and S2)—which explains why variation sites in *M. baileyi*, *M. cansus*, and *R. pruinosus* occur predominantly in non-domain regions (Fig. 1b). The p53–MDM2 interaction and MDM2/X E3 ligase activity are present in the common ancestor of vertebrates, the lamprey (Coffill et al., 2016; Levine, 2020), suggesting co-evolution of MDM2/X with the p53 pathway and preservation of a conserved cellular role throughout evolutionary history. Overall, MDM2 and p53 exhibit higher sequence homology within Spalacidae than MDMX does, and subterranean species show greater conservation compared with their aboveground orthologs, implying that p53–MDM2 functions are preserved in subterranean environments.

As mentioned above, *M. baileyi* and *M. cansus* live underground in the plateau, with extremely low oxygen and high carbon dioxide challenges for animal survival. We proposed that wild *M. baileyi* and *M. cansus* exhibit an evolutionary trade-off: optimizing hypoxia tolerance via hypoxia-inducible factor-1α (HIF-1α) (Chen et al., 2007) and MDM2/X, whereas laboratory rats prioritize genome integrity (ATM/ATR (ataxia-telangiectasia and Rad3-related protein)-MDM2/X) at the expense of hypoxia resistance. Subterranean species generally show enhanced hypoxia-related pathways—such as red blood cell function, blood vessel development, heart function, adenosine triphosphatase (ATPase) activity, and aerobic respiration (Deng et al., 2014; Shao et al., 2015; Hu et al., 2023). Notably, *M. baileyi* individuals living at high altitudes have evolved more finely-tuned patterns of hypoxia adaptation; zokors from different elevations showed altitude-dependent changes in gene transcription and cardiac-blood phenotypes (Cai et al., 2018; Wei et al., 2025). However, as members of the same rodent family (Spalacidae), bamboo rats (*R. pruinosus*) represent an intermediate model for hypoxia adaptation. In contrast to high-altitude zokors (*M. baileyi*/*M. cansus*), which endure extreme hypoxia, *R. pruinosus* inhabits subterranean burrows in tropical and subtropical regions—characterized by warmer, humid conditions and moderate oxygen limitation—while displaying greater stress resistance than aboveground rodents (Gao et al., 2023). *R. pruinosus* MDM2/X are convergent with those of *M. baileyi*, *M. cansus*, and *N. galili*, supporting a sister-group relationship between Myospalacinae (*M. baileyi*/*M. cansus* subfamily) and Rhizomyinae (*R. pruinosus* subfamily) based on genome analysis (Guo et al., 2021). Bamboo rats share many convergent genes with Chinese zokors and Israeli blind mole rats compared with aboveground controls; these genes are also enriched in the hypoxia-related pathways—such as response to oxidative stress, angiogenesis, and carboxylic acid transport (Ashur-Fabian et al., 2004; Gorbunova et al., 2012; Cao et al., 2020; Guo et al., 2021). However, *R. pruinosus* exhibits distinct physiological traits due to its specific life habits and herbivorous diet—centered on bamboo consumption—the larger body size of *R. pruinosus* relative to *M. baileyi*, *M. cansus*, and *N. galili* necessitates higher metabolic demands but is associated with slower respiration rates (Xiao et al., 2022; Gan et al., 2023). Therefore, *R. pruinosus* MDM2/X co-evolved with zokors yet introduce novel modifications, such as valine (V) at MDM2 codon 415—a substitution functionally analogous to alanine (A) in *M. baileyi*, *M. cansus*, and *N. galili*. The life ecology of bamboo rats is more similar to that of Israeli *Spalax*, characterized by intermittent hypoxic stress; they may exhibit flexible p53 reactivation following hypoxia and rely less on HIF than *M. baileyi*. Thus, the life-history traits of *M. baileyi*, *M. cansus*, and *R. pruinosus* shape diverse evolutionary dynamics underlying adaptation to the hypoxic subterranean environment.

3.2 Contribution of MDM2-mediated p53 functions to apoptosis

The transcription factor p53 plays a central role in the cellular stress response. Activated p53 regulates hundreds of target genes to determine cell fate—including DNA damage response, cell cycle

arrest, apoptosis, and senescence (Oren and Prives, 2024). In subterranean rodents, differential methylation levels of the *N. galili*-p53 promoter result in differential p53 expression, which selectively modulates adaptive cell-cycle arrest (Zhao et al., 2016). Meanwhile, we previously found that *M. baileyi*-p53 harbors a unique asparagine (N) substitution at codon 104 near the transactivation domain (TAD), responsible for the transactivation of apoptotic genes under environmental stresses. Under hypoxia (0.2% O_2), cold (30 °C), and acidic stress (pH 6.6), *M. baileyi*-p53 reduces the apoptosis rate by decreasing the mRNA expression of pro-apoptotic genes—B-cell lymphoma-2 (Bcl-2)-associated X protein (*Bax*), p53-upregulated modulator of apoptosis (*Puma*), and insulin-like growth factor-binding protein 3 (*Igfbp3*)—and upregulating *Bcl-2* levels (Zhao et al., 2013). We further observed high transcriptional and protein expression levels of both p53 and MDM2 in the lung and liver tissues of *M. baileyi* and *M. cansus* (Figs. 2 and 3); moreover, hypoxia induced *p53* mRNA expression via both the *M. baileyi*/*M. cansus*-MDM2 homodimer and MDM2/X heterodimer (Fig. 5a). Thus, accumulated *M. baileyi*/*M. cansus*-p53 contributes to anti-apoptotic activity under hypoxic conditions. The high co-expression of p53 and MDM2 further supports that *M. baileyi*/*M. cansus*-MDM2 is recruited for hypoxia survival, and extreme subterranean environments have driven the evolution of enhanced MDM2/X function. In *M. baileyi* and *M. cansus*, MDM2 and MDMX demonstrate functionally divergent yet cooperative roles in conferring hypoxia resistance. MDMX alone cannot recapitulate the functions of MDM2; data from MDMX mutations also failed to show changes in p53 expression or apoptosis. However, the MDM2/X heterodimer increases *p53* mRNA and enhances the regulation of p53 activity. Co-expression of *M. baileyi*-MDM2, MDMX, and p53 significantly reduced apoptosis under 0.1% O_2 hypoxic challenge, whereas *M. cansus*-MDM2 and p53 co-expression yielded a lower apoptosis rate. These findings suggested that evolutionary adaptations in wild subterranean rodents to extreme environments can reveal conserved mutation mechanisms with translational potential for drug design—mimicking nature's million-year selection process. Currently, MDM2 inhibitors, dual MDM2/MDMX inhibitors, and MDM2 degraders (PROTACs, an abbreviation for proteolysis targeting chimeras) are being explored for therapeutic antitumor and anti-inflammation applications (Fang et al., 2020; Zhang NY et al., 2023; Wang C et al., 2024; Wang W et al., 2024). However, challenges—including off-target side effects, acquired resistance, and systemic toxicity—persist in conventional laboratory models (rats or mice) (Peuget et al., 2024; Tuval et al., 2024); thus, studying natural adaptations may provide strategies to refine these therapeutic mechanisms.

The MDM2-MDMX-p53 axis exhibits striking functional differences between subterranean rodents (*M. baileyi* and *M. cansus*) and laboratory rats, reflecting their distinct evolutionary pressures and physiological demands. In addition, p53 dynamically regulates the balance between cell apoptosis and survival through MDM2 and MDMX. Wild *M. baileyi*/*M. cansus* maintains a well-balanced equilibrium, characterized by a higher apoptosis threshold, which confers resistance to hypoxia-induced cell death; laboratory rats, on the other hand, exhibit a lower apoptosis threshold, making them sensitive to DNA damage but robustly maintaining genome integrity.

3.3 MDM2 mutations at phosphorylation sites involved in p53 functions

Posttranslational modification plays an important role in the MDM2/X-p53 regulation. ATM, c-Abl, and checkpoint kinase 1/2 (Chk1/2) are critical kinases that regulate the phosphorylation of MDM2, MDMX, and p53 in response to DNA damage and hypoxia stress (Goldberg et al., 2002; Chen et al., 2005; Gajjar et al., 2012; Olcina et al., 2014; Carr et al., 2016; Hashimoto et al., 2018; Shi et al., 2020). The classical phosphosites, such as Hu-p53 Ser15, Hu-MDMX Ser403, and Hu-MDM2 Ser395 in humans, were highly conserved across species, including *M. baileyi* and *M. cansus* (Figs. S1–S3). However, we found two specific variations (F390 and A415) on the ATM/c-Abl-targeted phospho-sites in *M. baileyi*/*M. cansus*-MDM2, which might influence p53 stability and cell outcome decisions (Cheng et al., 2009, 2011; Karakostis et al., 2024).

Following stress, ATM phosphorylates MDM2 on six sites (Hu-MDM2 Ser386, Ser395, Ser407, Thr419, Ser425, and Ser429) between the acidic/zinc domain and RING domain (Gannon et al., 2012); and c-Abl activates Hu-MDM2 Tyr394 (Y394) (Goldberg et al., 2002; Carr et al., 2016). The target of MDM2-mediated ubiquitination shifts from p53 to the MDM2/MDMX heterodimer itself, which significantly disrupts p53 degradation and promotes p53 stabilization under stress

(Cheng et al., 2011; Pant and Lozano, 2014; Carr et al., 2016; Medina-Medina et al., 2016; Wu et al., 2024). We surprisingly found that MDM2 variation sites F390 and A/V415 (corresponding to Y and T in humans and rats) lack phosphorylation capability in Spalacidae species ranging from China to Israel (*M. baileyi*, *M. cansus*, *N. galili*, and *R. pruinosus*). The codon 415 encodes alanine (A)—a classical substitution associated with loss of phosphorylation—in *M. baileyi*, *M. cansus*, and *N. galili*, whereas *R. pruinosu* evolved a novel valine (V) substitution, which is electrically neutral at physiological pH and, like alanine, cannot be phosphorylated. In *M. baileyi*-MDM2 wt-A415, the hydrogen bond with E414 (corresponding to rat-MDM2 D414 and Hu-MDM2 E418) is lost; in contrast, such a hydrogen bond is present between rat-MDM2 D414 and T415 (Hu-MDM2 E418 and T419) (Fig. S4b$_3$). Meanwhile, the F390 substitution is phenylalanine across all four Spalacidae species (*M. baileyi*, *M. cansus*, *N. galili*, and *R. pruinosus*). In *M. baileyi*-MDM2 wt-F390, a hydrogen bond forms with S391 (rat-MDM2 S391 and Hu-MDM2 S395—the canonical ATM phospho-site), whereas no such bond occurs between rat-MDM2 Y390 and S391 (Hu-MDM2 Y394 and S395) (Fig. S4b$_2$). These alterations in hydrogen bonding may reduce structural stability and perturb native conformations.

The disordered regions exist as dynamic ensembles of interconverting conformations with intrinsically unstable 3D structure; they are essential for transcriptional control, cell signaling, and subcellular organization (Holehouse and Kragelund, 2024). MDM2 degrades p53 by tightly binding to the p53 dimer. The F390 and A415 substitutions in this disorder region lead to distinct MDM2 conformations between *M. baileyi* and rat (Fig. S4b$_1$) and destabilize the C-terminal portion of MDM2 in the *M. baileyi*-p53 dimer-MDM2 complex (Fig. S4c). The sequences and structures of the canonical N-terminal p53–MDM2 interaction region—the p53 transactivation domain, including the BOX-I motif—are conserved among rat, *M. baileyi*, and *M. cansus* (Figs. S3 and S5a) (Padariya et al., 2022). Therefore, the F390 and A415 substitutions in the C-terminal disordered region of *M. baileyi*-MDM2 may impair p53 ubiquitination.

In humans, Hu-MDM2 Y394 and T419 (corresponding to *M. baileyi*-MDM2 F390 and A415) are redundant in MDM2-p53 signaling due to their non-canonical ATM- and c-Abl-mediated phosphorylation (Goldberg et al., 2002; Cheng et al., 2009, 2011; Carr et al., 2016). However, our findings show that natural *M. baileyi*/*M. cansus*-MDM2 variants F390 and A415 increase p53 expression at both the mRNA and protein levels; by contrast, artificial mutations (F390Y and A415T) restore phosphorylation capacity but block p53 accumulation in zokors. These results suggest that the *M. baileyi*/*M. cansus*-MDM2 variants disrupt ATM/c-Abl-mediated phosphorylation under subterranean conditions, thereby establishing a unique dynamic balance between p53 accumulation and apoptosis suppression in zokors. Therefore, subterranean species have evolved a uniquely adaptive p53-MDM2/X axis to favor cell survival.

4 Conclusions

The MDM2-MDMX-p53 axis in wild subterranean rodents exemplifies evolutionary innovation under extreme environmental conditions, whereas laboratory rats retain the ancestral mammalian regulatory mechanism. The evolution of *Mdm2*, *Mdmx*, and *p53* genes, as well as their specialized regulatory loop, divergently shapes stress responses in subterranean versus aboveground species, yet ultimately converges on a shared survival outcome under stress. These natural evolutionary modifications of molecular mechanisms highlight how gene networks can be repurposed when survival takes precedence over tumor suppression. This has important implications for evolutionary biology, stress adaptation, and medicine.

Materials and methods

Detailed methods are provided in the electronic supplementary materials of this paper.

Data availability statement

All data supporting the findings of this study are contained within the paper and supplementary materials.

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Author contributions

Xuequn CHEN, Yang ZHAO, and Jizeng DU designed the research and supervised the study. Mengchen ZHANG, Eviatar NEVO, Yang ZHAO, and Xuequn CHEN wrote the manuscript. Mengchen ZHANG and Yi LI performed molecular and cellular experiments and statistical analyses. Huiqi LIN and Fangyuan XIA contributed to genetic evolutionary analysis. Tianfu YU, Mahanand CHATOO, Kexin LI, Honghao YU, Yang ZHAO, Eviatar NEVO, and Xuequn CHEN collected *Nannospalax galili*, *Myospalax baileyi*, *Myospalax cansus*, and *Rhizomys pruinosus* animal samples. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Mengchen ZHANG, Yi LI, Huiqi LIN, Tianfu YU, Fangyuan XIA, Mahanand CHATOO, Kexin LI, Honghao YU, Eviatar NEVO, Jizeng DU, Yang ZHAO, and Xuequn CHEN declare that they have no conflicts of interest.

All experiments were performed in accordance with the Guide for the Care and Use of Laboratory Animals and were approved by the Laboratory Animal Welfare and Ethics Committee of Zhejiang University, Hangzhou, China (Certificate No. ZJU20220102).

Declaration on the use of generative AI tools

No generative AI tools were used in the preparation of this manuscript.

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Supplementary information

Materials and methods; Table S1; Figs. S1–S5