Polyamine Depletion Increases Cytoplasmic Levels of RNA-binding Protein HuR Leading to Stabilization of Nucleophosmin and p53 mRNAs*

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Polyamines are essential for maintaining normal intestinal epithelial integrity, an effect that relies, at least in part, on their ability to keep low levels of nucleophosmin (NPM) and p53 mRNAs. The RNA-binding protein HuR associates with the p53 mRNA, as reported previously, and with the NPM mRNA, computationally predicted to be a target of HuR. Here, we show that HuR binds the NPM and p53 3′-untranslated regions and stabilizes these mRNAs in polyamine-depleted intestinal epithelial cells. Depletion of cellular polyamines by inhibiting ornithine decarboxylase with α-difluoromethylornithine dramatically enhanced the cytoplasmic abundance of HuR, whereas ectopic ornithine decarboxylase overexpression decreased cytoplasmic HuR; neither intervention changed whole-cell HuR levels. HuR was found to specifically bind the 3′-untranslated regions of NPN and p53 mRNAs. HuR silencing rendered the NPM and p53 mRNAs unstable and prevented increases in NPM and p53 mRNA and protein in polyamine-deficient cells. These results indicate that polyamines modulate cytoplasmic HuR levels in intestinal epithelial cells, in turn controlling the stability of the NPM and p53 mRNAs and influencing NPM and p53 protein levels.

The mammalian intestinal epithelium is a rapidly self-renewing tissue in the body, and its homeostasis is preserved through strict regulation of epithelial cell proliferation, growth arrest, and apoptosis (1–3). Under physiological conditions, the epithelium of the human small intestine undergoes ≈1011 mitoses per day (4). This dynamic renewal is highly regulated and critically controlled by numerous factors, including cellular polyamines (1, 5, 6). The natural polyamines spermidine and spermine and their precursor putrescine are organic cations found in all eukaryotic cells (7). The regulation of cellular polyamines is thought to be a central convergence point for the multiple signaling pathways driving epithelial cell function. We (6, 8–14) and others (1, 5, 15) have demonstrated that normal epithelial cell proliferation in the intestinal mucosa depends on the supply of polyamines to the dividing cells and that decreasing cellular polyamines inhibits epithelial cell proliferation by stabilizing the mRNAs that encode nucleophosmin (NPM),3 p53, and other growth-inhibiting factors. However, the exact mechanisms whereby polyamine depletion stabilizes NPM and p53 mRNAs remain elusive.

Although gene expression is crucially modulated by transcription, the essential contribution of posttranscriptional events, such as mRNA processing, transport, turnover, and translation, is becoming increasingly recognized. In particular, altered mRNA turnover is shown to play a critical role in the activation of specific genes during the cellular response to mitogens, immunological triggers, stressful stimuli, and differentiation agents (16, 17). mRNA turnover is primarily controlled through the association of RNA-binding proteins that bind to specific RNA sequences and either increase or decrease the transcript half-life and thus alters the profiles of expressed gene products (18, 19). The best characterized cis-acting elements of mRNA turnover are U- and AU-rich elements located in the 3′-untranslated regions (3′-UTRs) of many labile mRNAs, such as those of certain protooncogenes, cytokines, and cell cycle regulatory proteins (19). The RNA-binding protein HuR prominently regulates gene expression through binding to mRNAs, which typically bear one or several hits of a recently described RNA motif (45) that resembles an AU-rich element. Upon binding to a target mRNA, HuR has been shown to stabilize it, alter its translation, or perform both functions (18–22). HuR is predominantly nuclear in unstimulated cells but translocates to the cytoplasm in response to various stimuli (20–22,47). Although the precise processes regulating HuR function

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3 The abbreviations used are: NPM, nucleophosmin; ODC, ornithine decarboxylase; UTR, untranslated region; DFMO, DL-α-difluoromethylornithine; CR, coding region; siRNA, small interfering RNA; siHuR, siRNA targeting HuR mRNA; IEC, intestinal epithelial cells; Q-PCR, quantitative PCR; RT, reverse transcription; IP, immunoprecipitation; AMPK, AMP-activated protein kinase; PUF, putrescine; TGF, transforming growth factor; RNP, ribonucleoprotein.
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remain to be fully understood, its subcellular localization is intimately linked to its effects upon target transcripts.

We (12, 14) recently showed that depletion of cellular polyamines by inhibiting the activity of ornithine decarboxylase (ODC, the first rate-limiting enzyme for polyamine biosynthesis (7)) with its specific inhibitor DL-α-difluoromethylornithine (DFMO) dramatically stabilized NPM and p53 mRNAs and increased the rate of newly synthesized NPM and p53 proteins, thereby inhibiting the proliferation of intestinal epithelial cells.

Given the affinity of HuR for the p53 mRNA (21) and the predicted association of HuR with NPM mRNA (45), we sought to directly investigate whether polyamines modulated HuR function in intestinal epithelial cells and whether HuR influenced the abundance of NPM and p53 mRNA and protein levels. The data presented herein demonstrate that a decrease in the levels of cellular polyamines induced the cytoplasmic accumulation of HuR, whereas increasing cellular polyamines enhanced its nuclear concentration. Furthermore, the increased stabilization of NPM and p53 mRNAs was found to be functionally linked to the interaction of their 3′-UTRs with cytoplasmic HuR following polyamine depletion.

MATERIALS AND METHODS

Chemicals and Supplies—Tissue culture medium and diazyzed fetal bovine serum were from Invitrogen, and biochemicals were from Sigma. The antibody recognizing HuR was from Santa Cruz Biotechnology (Santa Cruz, CA), and those recognizing NPM and p53 proteins were from Clontech. DFMO was from Ilex Oncology Inc. (San Antonio, TX).

Cell Culture and Stable ODC Gene Transfection—The IEC-6 cell line, derived from normal rat intestinal crypt cells (23), was purchased from the American Type Culture Collection at passage 13 and used at passages 15–20 (13, 24). Cells were maintained in Dulbecco’s modified Eagle’s medium supplemented with 5% heat-inactivated fetal bovine serum, 10 μg/ml insulin, and 50 μg/ml gentamicin. ODC-overexpressing IEC-6 (ODC-IEC) cells were developed as described (25) and expressed a more stable ODC variant with full enzyme activity (26).

RNA Interference—The silencing RNA duplexes used (5′-AACACGGCTGACGCCTTGAGG-3′ (targeting HuR) and 5′-AAGTGATAGTAGATCCACGGC-3′ (control small interfering RNA (siRNA)) were transfected with Lipofectamine (20 μl final siRNA) and harvested for analysis 48 h later.

RT-PCR and Real-time PCR Analysis—Total RNA was isolated by using RNaseasy mini kit (Qiagen, Valencia, CA) and used in reverse transcription and PCR amplification reactions as described (14, 28). PCR primers for NPM were 5′-CGATGGA-CATGGACATGAC-3′ (sense) and 5′-TTCCTCTACGC-TACTAGT-3′ (antisense), yielding a 238-bp fragment (14). Primers for p53 were purchased from R&D Systems Inc. (Minneapolis, MN) and yielded a 397-bp fragment. The levels of β-actin PCR product were assessed to monitor the even RNA input in RT-PCR samples. Real-time quantitative PCR (Q-PCR) was performed using an Applied Biosystems instrument (Foster City, CA) using specific primers, probes, and software (Applied Biosystems). The levels of NPM and p53 mRNAs were quantified by Q-PCR analysis and normalized glyceraldehyde-3-phosphate dehydrogenase levels.

Preparation of Synthetic RNA Templates—Complementary DNA from IEC-6 cells was used as a template for PCR amplification of the coding region (CR) and 3′-UTR of NPM and p53. The 5′ primers contained the T7 RNA polymerase promoter sequence (T7): 5′-CCAAGCTTCTAATAGCCTCATTAGGGAGA-3′. To prepare the CR of NPM (positions 97–1300), oligonucleotides (T7)5′-ATGGAAGATTCTTGAGACATGGACATGAC-3′ and 5′-ATGGGATCCTTCTAGATTTCTTC-3′ were used. To prepare the NPM 3′-UTR template (spanning positions 771–1300), oligonucleotides (T7)5′-AGAATCCTTCAA-GAACAGC-3′ and 5′-TACTTATTAAATACTGAG-3′ were used. To prepare the CR of p53 (positions 252–1439), oligonucleotides (T7)5′-ATGGGAGACCGCAGTCATGCTAGC-3′ and 5′-AGAATGTCATGCTAGTACGAGC-3′ were used. To prepare the p53 3′-UTR template (positions 1421–2629), oligonucleotides (T7)5′-TGACTCAGACTGAC-ATCTTCC-3′ and 5′-TGAGCAGAATTTTTAGTTGAAAATAAGAGATCG-3′ were used. PCR-amplified products were used as templates to transcribe biotinylated RNAs by using T7 RNA polymerase in the presence of biotin-cytidine 5′-triphosphate as described (21).

RNA-Protein Binding Assays—For biotin pull-down assays, biotinylated transcripts (6 μg) were incubated with 120 μg of cytoplasmic lysate for 30 min at room temperature. Complexes were isolated with paramagnetic streptavidin-conjugated Dynabeads (Dynal, Oslo, Norway) and analyzed by Western blotting. To assess the association of endogenous HuR with endogenous NPM and p53 mRNAs, immunoprecipitation (IP) of endogenous HuR-mRNA complexes was performed as described (21, 29). Twenty million IEC-6 cells were collected per sample, and lysates were used for IP for 4 h at room temperature in the presence of excess (30 μg) IP antibody (IgG or anti-HuR). RNA in IP materials was used in RT followed by PCR or Q-PCR analysis to detect the presence of NPM and p53 mRNAs.

Immunofluorescence Staining—Immunofluorescence was performed according as described (30) with minor changes (14). Cells were fixed using 3.7% formaldehyde, and the rehydrated samples were incubated overnight at 4 °C with primary antibody anti-HuR diluted 1:300 in blocking buffer and then incubated with secondary antibody conjugated with Alexa Fluor-594 (Molecular Probes, Eugene, OR) for 2 h at room temperature. After rinsing, slides were incubated with 1 μM TO-PRO3
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Polyamine Depletion in IEC-6 Cells Enhances Cytoplasmic HuR Levels—Since HuR was predicted to bind the NPM 3' UTR (21) and was predicted to bind the NPM 3' UTR (41, 45), we sought to formally investigate whether HuR was involved in the polyamine-dependent regulation of these mRNAs. Consistent with our previous studies (10, 11), exposure of IEC-6 cells to 5 mM DFMO for 4 and 6 days completely inhibited ODC with our previous studies (10, 11), exposure of IEC-6 cells to 5 mM DFMO for 4 and 6 days completely inhibited ODC activity and depleted cellular polyamines. Putrescine and spermidine were undetectable at 4 and 6 days after treatment with DFMO, and spermine had decreased by ~60% (not shown). Treatment with DFMO for 4 or 6 days significantly enhanced cytoplasmic HuR levels (by 1.7- and 3.8-fold, respectively), reduced its nuclear abundance, and did not change its whole-cell levels (Fig. 1, A and B). Supplementation with the polyamine putrescine (10 μM) reversed the DFMO-triggered changes in HuR subcellular distribution, as did spermidine supplementation (data not shown). To monitor the quality and abundance of the nuclear and cytoplasmic fractions, we examined the levels of lamin B (a nuclear protein, Fig. 1A) and β-tubulin (a cytoplasmic protein, not shown), respectively. Assessment of these markers revealed that there was no contamination between cytoplasmic and nuclear fractions. These changes in HuR subcellular distribution were further studied by immunofluorescence staining. Consistent with the Western blotting results, HuR immunostaining was almost undetectable in the cytoplasm of untreated cells (Fig. 1C, panel a), but it increased significantly in DFMO-treated cells (Fig. 1C, panel b), associated with a decrease in its nuclear levels. Combined treatment with DFMO and putrescine prevented the increased cytoplasmic HuR signal, rendering a subcellular staining pattern similar to that of untreated cells (Fig. 1C, panel c). These results indicate that lowering cellular polyamines increased the cytoplasmic levels of HuR in intestinal epithelial cells.

Increasing Cellular Polyamines by ODC Overexpression Inhibits the Cytoplasmic Levels of HuR—We employed two clones of stable ODC-expressing cells recently developed in our laboratory that exhibited high levels of ODC protein (Fig. 2, A and B) and greater than 50-fold increase in ODC enzyme activity (Fig. 2A, panel a) and elevated cellular polyamines putrescine, spermidine, and spermine (by 12-fold, 2-fold, and 25% when compared with control populations, respectively; not shown). ODC overexpression decreased the levels of cytoplasmic HuR by ~50% (from 1.05 ± 0.03 in controls to 0.47 ± 0.02 in ODC-IEC-C1 and 0.49 ± 0.02 in ODC-IEC-C2; n = 3, p < 0.05) and correspondingly increased its nuclear abundance; no net changes in whole-cell HuR levels were seen in ODC-IEC cells

FIGURE 1. Changes in levels and cellular distribution of HuR in control IEC-6 cells and in cells treated with either DFMO (5 mM) alone or DFMO plus PUT (10 μM) for 4 and 6 days. Whole-cell lysates, cytoplasmic, and nuclear lysates were prepared for Western blotting. A, representative Western blots. Panel a, cytoplasmic proteins; panel b, nuclear proteins; and panel c, total proteins. Cytoplasmic, nuclear, and total proteins (30 μg of each) were subjected to SDS-PAGE (10% acrylamide). After detecting HuR (~34 kDa), blots were reprobed to detect β-actin (~42 kDa) in cytoplasmic and whole-cell lysates or lamin B in nuclear lysates to control for the quality of the fractionation procedure and the even loading of samples. B, quantitative analysis derived from densitometric scans of immunoblots of cytoplasmic HuR as described for A. Panel a. Values are the means ± S.E. from three separate experiments. *p < 0.05 when compared with controls and cells treated with DFMO plus PUT. C, cellular distribution of HuR in cells described in A, panel a, control; panel b, DFMO treatment for 6 days; and panel c, DFMO + PUT treatment for 6 days. After HuR immunostaining (see "Materials and Methods"), nuclei were visualized with TO-PRO3. Purple, HuR; yellow, nuclei. Original magnification, ×1,000. Three experiments were performed that showed similar results.
when compared with control cells (Fig. 2B). The effect of ODC overexpression on the subcellular distribution of HuR was not simply due to clonal variation since two stable clones, ODC-IEC-C1 and ODC-IEC-C2, showed identical responses. These results suggest that increasing cellular polyamines promotes the nuclear accumulation of HuR and reduces its cytoplasmic levels in intestinal epithelial cells.

**FIGURE 2. Changes in HuR protein in stable ODC-IEC cells.** A, expression of ODC in clonal (C1 and C2) populations of IEC cells stably overexpressing ODC (ODC-IEC) and in control IEC-6 cells (Vector alone). Panel a, ODC protein, and panel b, ODC enzyme activity. *, p < 0.05 when compared with cells infected with a control vector. B, representative Western blot analysis of cells described in A. Panel a, cytoplasmic proteins; panel b, nuclear proteins; and panel c, total proteins. Whole-cell lysates were harvested, cytoplasmic and nuclear fractions prepared, and HuR was detected by Western blot analysis. β-Actin signals served to assess the equality of protein loading in cytoplasmic and whole-cell lysates; lamin B served to assess immunoblotting of nuclear lysates.

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**FIGURE 3. Binding of cytoplasmic HuR to NPM transcripts.** A, schematic representation of NPM mRNA and the AU-rich sequences in its 3'-UTR. B, cytoplasmic lysates (120 μg of each) prepared from control, DFMO-treated, or DFMO + PUT-treated cells (4 and 6 days) were incubated with 6 μg of biotinylated NPM 3'-UTR or CR for 30 min at 25 °C, and the resulting RNP complexes were pulled down by using streptavidin-coated beads. Panels a and b, representative HuR immunoblots using the pull-down materials from the 3'-UTR (panel a) or CR (panel b). Three experiments were performed that showed similar results.

*Cytoplasmic HuR Directly Binds the NPM and p53 3'-UTRs—Based on the association of HuR with the p53 mRNA (21) and its predicted affinity for the NPM mRNA (45) at their 3'-UTRs (Figs. 3A and 4A), we hypothesized that the NPM and p53 3'-UTRs bound HuR in IEC-6 cells and further postulated that this association would increase in the cytoplasm following polyamine depletion. To test these possibilities, we performed two experiments. First, we used biotinylated transcripts spanning the NPM or p53 3'-UTRs in RNA pull-down assays (see “Materials and Methods”) using cell lysates prepared from either untreated or polyamine-deficient cells. The NPM 3'-UTR transcript readily associated with cytoplasmic HuR, as detected by Western blot analysis of the pull-down material (Fig. 3B); the binding intensity increased significantly when using lysates prepared from cells that were treated with DFMO for 4 or 6 days.*
days (by 1.8- and 3.3-fold, respectively) but was reduced when cells had been treated with putrescine. Importantly, transcripts corresponding to the CR of NPM did not bind to HuR (Fig. 3B, panel b). Similarly, HuR binding to the p53 3′-UTR (but not the CR) also increased by 2.4- and 2.9-fold when using lysates prepared from DFMO-treated cells (Fig. 4B, panel a, and B, panel b). Again, administration of putrescine together with DFMO completely prevented this elevation in binding.

Second, we examined the in vivo association of endogenous NPM and p53 mRNAs with HuR in IEC-6 cells following polyamine depletion through IP of HuR under conditions that preserved its association with target mRNAs in ribonucleoprotein (RNP) complexes. The RNP complexes immunoprecipitated using anti-HuR antibody did contain endogenous NPM and p53 mRNAs, as measured by conventional PCR and real-time (Q-PCR) analyses (Fig. 5, A and B). The association of endogenous NPM and p53 mRNAs with endogenous HuR increased significantly (~4.6 and ~5.3 times) in DFMO-treated cells.

Importantly, the NPM and p53 mRNAs were undetectable or dramatically reduced in nonspecific IgG1 IPs (Fig. 5A, right). Together, these findings support the notion that cytoplasmic HuR in intestinal epithelial cells specifically binds to the 3′-UTRs of NPM and p53 and that binding increases following polyamine depletion.

HuR Silencing Abolishes the Increased Stability of NPM and p53 mRNAs in Polyamine-deficient Cells—We used small interfering RNA (siRNA) targeting the HuR mRNA (siHuR) to reduce HuR levels and thus directly examine its putative role in the previously reported changes in NPM and p53 mRNA stability following polyamine depletion (12, 14). With >95% cells transfected (data not shown), siHuR potently and specifically silenced HuR expression in polyamine-deficient cells (by ~80% at 48 h after transfection, Fig. 6A). Consistent with our previous findings showing that polyamine depletion stabilized the NPM and p53 mRNAs (12, 14), the half-lives of NPM and p53 mRNAs in DFMO-treated cells increased dramatically; the increased stability of NPM and p53 mRNAs in polyamine-deficient cells was abolished by silencing HuR (Fig. 6B) as the half-lives of NPM and p53 mRNAs in DFMO-treated siRNA-transfected
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**A**

![Image](146x254 to 225x278)

**B**

![Image](147x578 to 225x607)

**C**

![Image](148x612 to 225x667)

**FIGURE 6.** Effect of HuR silencing on the expression and stability of NPM and p53 mRNAs. A, representative HuR immunoblots. After DFMO treatment (4 days), cells were transfected with either control siRNA (C-siRNA) or siHuR, and whole-cell lysates were harvested 48 h thereafter. The levels of HuR protein were measured by Western blot analysis, and equal loading was monitored by β-actin immunoblotting. B, half-life of the NPM mRNA (panel a) and p53 mRNA (panel b), assessed by using 5 μg of actinomycin D/ml. Total cellular RNA was isolated at the times shown, and the remaining levels of NPM, p53, and β-actin mRNAs were measured by Q-PCR analysis. Values are the means ± S.E. from triplicate samples. *, p < 0.05 when comparing control and DFMO-treated cells transfected with siHuR. C, changes in expression of NPM and p53 proteins as measured by Western blot analysis in cells that were processed as described in A. Data are representative from three independent experiments showing similar results.

cells were similar to those of control cells (without DFMO). Furthermore, in HuR-silenced populations, the increased NPM and p53 protein levels following polyamine depletion were also prevented (Fig. 6C) and were reduced to the levels observed in control populations. Transfection with control siRNA had no effect on the stability of the NPM and p53 mRNAs or the levels of the corresponding proteins in polyamine-deficient cells. These findings strongly suggest that HuR critically contributes to the increased stability of NPM and p53 mRNAs in polyamine-depleted cells, in turn elevating NPM and p53 expression and thereby contributing to the inhibition of intestinal epithelial cell proliferation (11–14).

**DISCUSSION**

Although the molecular mechanisms whereby polyamines control the growth of intestinal mucosal cells have not been fully elucidated, they are known to be involved in the regulation of growth-related genes (8, 9, 13, 32, 33). In this regard, polyamines have been shown to suppress the expression of growth-inhibiting genes such as p53 (10, 12), NPM (14), p21 (34), TGFβ/TGFβ-Rs (TGFβ-receptors) (8, 35), and junD (11, 39), primarily by controlling mRNA stability. Our previous studies showed that increases in the levels of cellular polyamines reduce the stability, and hence the steady-state abundance, of the NPM and p53 mRNAs, whereas decreases in cellular polyamines activate the expression of the NPM and p53 genes by stabilizing their mRNAs, in turn leading to increased arrest in the G1 phase of the cell cycle (12, 14). The present studies implicate HuR in these processes, thereby advancing our understanding of the regulation of NPM and p53 expression in intestinal epithelial cells.

A significant body of literature has indicated that HuR-mediated transcript stabilization and translational control are closely linked to its cytoplasmic presence (18, 19, 46). Here, DFMO-mediated depletion of cellular polyamines significantly induced the cytoplasmic accumulation of HuR but did not alter whole-cell HuR levels (Fig. 1). The specificity of these effects was demonstrated by the addition of exogenous putrescine, which completely prevented the cytoplasmic increase in HuR levels. Furthermore, ectopic ODC overexpression increased cellular polyamines and decreased the levels of cytoplasmic HuR, whereas it increased HuR in the nucleus (Fig. 2). Polyamines have been shown to influence multiple distinct signaling pathways leading to alterations of gene transcription (9, 32), posttranscriptional events (8, 11), protein phosphorylation (36), and protein trafficking (24, 37), including the nuclear import of transcription factors such as NF-κB (37, 38), Smads (24), and JunD (11, 39). Although it remains to be formally shown that the role of HuR in the stabilization of NPM and p53 mRNAs in polyamine-deficient cells is linked to the cytoplasmic localization of HuR RNP complexes, our studies show that the cytoplasmic HuR specifically binds to 3'-UTR of NPM and p53 mRNAs following polyamine depletion. These findings are further supported by evidence that the endogenous NPM and p53 mRNAs associate with the endogenous HuR in the materials immunoprecipitated by anti-HuR antibody (Fig. 5) and further suggest that polyamine depletion increases HuR function in intestinal epithelial cells. How polyamines influence HuR abundance in the cytoplasm remains an open question, but we have preliminary evidence that supports the involvement of the AMP-activated protein kinase (AMPK), a kinase previously shown to inhibit the cytoplasmic export of HuR (50). Interven-
tions to decrease cellular polyamines significantly reduced AMPK enzyme activity, whereas ectopic constitutive activation of AMPK prevented the elevation in cytoplasmic HuR levels in polyamine-deficient cells. The precise mechanisms by which polyamines modulate AMPK function and HuR distribution are the focus of our ongoing studies.

Our observations are also consistent with studies demonstrating that HuR binds to AU-rich elements commonly found in the 3′-UTRs of labile mRNAs (40, 42–44), and in particular, mRNAs bearing a recently identified RNA motif in HuR target transcripts (45, 47). The p53 mRNA contains several hits for the HuR motif and was formally shown to be a target of HuR (21). Those studies were performed in human colon carcinoma cells and implicated HuR in a target of HuR (21). Those studies were performed in human colon carcinoma cells and implicated HuR in enhancing the translation of the p53 mRNA, not its stability; it remains to be investigated whether the effects of HuR on target mRNAs are cell type-specific and whether the translation of p53 is also influenced by HuR in IEC cells. Computational analysis of the NPM mRNA revealed that its 3′-UTR also has a HuR motif hit, thus making it a putative HuR target, as confirmed here. Future studies in polyamine-deficient cells must address the possible role of HuR in the stabilization of other mRNAs such as those encoding the aforementioned growth inhibitory genes p21 and TGF-β, encoded by mRNAs, which are also targets of HuR (45, 49).

The transcript stability data presented in Fig. 6 further show that HuR levels critically influence NPM and p53 mRNA stability in polyamine-deficient cells. In keeping with our previous results (12, 14), polyamine depletion increased the half-life of NPM and p53 mRNAs, but this effect was abrogated in cells in which HuR expression was reduced by RNA interference, NPM and p53 mRNAs, and thereby contribute to maintaining the integrity of the intestinal epithelium under physiological and pathological conditions.

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