Long non-coding RNA ROR mitigates cobalt chloride-induced hypoxia injury through regulation of miR-145

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ABSTRACT
Obstructive sleep apnoea-hypopnoea syndrome (OSAHS) is a condition causing apnea and hypopnea. LncRNA-ROR revealed properties in regulating hypoxia response. Our study explored the roles of ROR in CoCl2-induced hypoxia injury in HK-2 cells. HK-2 cells were treated with CoCl2 to induce hypoxia injury. Cell viability, cell apoptosis and apoptotic proteins were detected using CCK-8, flow cytometry and western blot, respectively. The alter expression of ROR and miR-145 was achieved through transfection. Moreover, the expressions of HIF-α and ERK and MAPK related factors were examined using western blot. We found that CoCl2 decreased cell viability and increased apoptosis as well as increased the expression of ROR. ROR overexpression increased cell viability, decreased cell apoptosis. ROR overexpression upregulated anti-apoptotic proteins Bcl-2 and decreased p53, Bax and cleaved-Caspase-3. ROR overexpression also increased the expression of HIF-α. On the opposite, ROR silence led to the opposite results as relative to ROR overexpression. ROR overexpression decreased expression of miR-145. Co-transfection with ROR overexpression and miR-145 impaired the promoting effects of ROR in CoCl2 treated cells. ROR increased phosphorylation of ERK while decreased phosphorylation of MAPK. In conclusion, lncRNA ROR alleviated CoCl2-induced hypoxia injury through regulation of miR-145 as well as modulating ERK and MAPK signalling.

HIGHLIGHTS
1. CoCl2 induces ROR upregulation;
2. Overexpression of ROR reduces CoCl2-induced HK-2 cell injury;
3. Silence of ROR promotes CoCl2-induced HK-2 cell injury;
4. Overexpression of ROR decreases miR-145 expression;
5. ROR overexpression modulates ERK and MAPK signalling pathways through regulation of miR-145.

Introduction
Obstructive sleep apnoea-hypopnoea syndrome (OSAHS) is a condition in which the pharyngeal airway collapses and blocks during sleep, causing apnea and hypopnea [1,2]. It is usually associated with snoring, sleep disorders, frequent oxygen desaturation during sleep, daytime sleepiness and inattention [3]. Current studies have shown that recurrent apnea during sleep and/or shallow breathing, as well as recurrent hypoxemia, hypercapnia and sleep disorders at night can lead to impaired renal function, further researches pointed out that long time OSAHS could induce serious diseases such as hypertension, myocardial infarction and stroke [2,3]. In the past years, treatment with OSAHS has not received enough attention due to wrong idea about this disease. Therefore, except continuous positive airway pressure approach [4], even some researches also point out to use mandibular advancement devices [5]. However, no breakthrough was made in the treatment of OSAHS. Therefore, novel and effective treatment was urgently needed and deeper understanding about OSAHS is also requisite.

Nowadays, using molecular approach, such as IncRNAs to resolve some diseases are becoming popular [6]. Scientists started to search for the disease-related IncRNAs to looking for novel approach for the understating or even treatment of respiratory diseases [7]. For example, IncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) silence promoted cell apoptosis in neonatal respiratory distress syndrome [8]. In these IncRNAs, regulator of reprogramming (ROR) is prominently found in malignant cancers, in which IncRNA-ROR mainly exerts as a key competing endogamous miRNA sponge promoting to cancer development [9,10]. In addition, IncRNA ROR was also known as a suppressor for p53 expression in response to DNA damage and ROR could also regulate cell apoptosis [11,12]. Combined with the above information, we aimed to explore whether IncRNA was con

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activation of inflammatory pathways and hypoxia injury was involved [13,14]. Therefore, in our study, we used cobalt chloride (CoCl₂) to stimulate HK-2 cells to establish an OSAHS cell model in vitro.

In addition, IncRNAs are often found to cooperate with miRNAs to regulate biological progression in transcription level [15]. miR-145 is often used in various inflammatory progressions in Asthma as well as in chronic obstructive pulmonary disease (COPD) [16]. Is there possible that miR-145 was also involved in OSAHS? Or even whether miR-145 could cooperate with lncRNA ROR? This is what our study explored. In our study, we explored the roles of ROR in CoCl₂ to stimulate HK-2 cells and the underlying mechanism by which ROR achieved its functions.

Material and methods

Reagents and cell culture

Reagents: Roswell Park Memorial Institute (RPMI)-1640 (Gibo, Grand Island, Newyork, USA), fetal bovine serum (FBS; Life Science, UT, USA), 100 U/ml penicillin and 0.1 mg/ml streptomycin (Sigma-Aldrich, St. Louis, USA).

Cell culture: HK-2 cells were provided by Riken cell bank (Ibaraki, Japan). HK-2 cells were digested routinely and centrifuged at 100,000 g for 5 min. Then, cells were washed with phosphate-buffered saline (PBS) for two times, and then slowly added with 500 µl binding buffer. Cells were gently shaken and resuspended. Fluorescein isothiocyanate (FITC)-conjugated Annexin V and propidium iodide (PI) 5 µl staining were added to the cell suspension. After that, the apoptotic cell’s rate was determined with flow cytometer (Beckman Coulter, USA) following the manufacturer’s instruction.

Cell viability assay

HK-2 cells in logarithmic growth phase were collected and subcultured in 96-well plate at the density of 10,000 cells in each well. After one night time, then the culture medium was changed. 10 µl cell counting kit-8 (CCK-8) solution was added to each well at 37°C for 1 h. In the end, absorption values were obtained using a Microplate Reader (Bio-Rad, Hercules, CA) at 450 nm.

Cell apoptosis assay

HK-2 cells were digested routinely and centrifuged at 100 x g for 5 min. Then, cells were washed with phosphate-buffered saline (PBS) for two times, and then slowly added with 500 µl binding buffer. Cells were gently shaken and resuspended. Fluorescein isothiocyanate (FITC)-conjugated Annexin V and propidium iodide (PI) 5 µl staining were added to the cell suspension. After that, the apoptotic cell’s rate was determined with flow cytometer (Beckman Coulter, USA) following the manufacturer’s instruction.

Western blot

HK-2 cells were collected and using RIPA lysis buffer (Article No: R0010, Solarbio, Beijing, China) for cell lysis. The BCA™ Protein Assay Kit (Pierce, Appleton, WI, USA) was used for detecting protein quantification. Bio-Rad Bis-Tris Gel system was applied for constructing western blot system. Primary antibodies (Abcam, Cambridge, UK) were maintained in the dark at 4°C overnight and the membrane was washed the next day. Secondary antibody incubates with horseradish peroxidase (HRP) conjugated and the bands were quantified by Image Lab™ Software (Bio-Rad, Shanghai, China).

Quantitative real-time polymerase chain reaction (qRT-PCR)

Total RNA was extracted using TRizol reagent (Invitrogen) and was reverse transcribed into cDNA using a Reverse Transcription Kit (Takara, Dalian, China) according to the manufacturer’s instructions. The expression of ROR was conducted by qRT-PCR using the SYBR Green Master Mix (Takara) according to the manufacturer’s instruction. The mRNA of GAPDH level was used as an internal control and relative expression changes were calculated using the 2-ΔΔCt method.

The TaqMan MicroRNA Assay was employed to determine the expression of miR-145 (Applied Biosystems, Foster City, CA, USA). The expression of miR-145 was normalized to U6 snRNA.

Cell transfection

In order to alter the expression of genes, miR-145 mimic and their corresponding negative control (NC); another group pcROR and si-ROR (GenePharma Co., Shanghai, China) were transfected into HK-2 cells. Cells were transfected with miR-145 mimic using Lipofectamine 2000 reagent (Invitrogen).

Statistical analysis

All the results were shown by mean ± standard deviation (SD). Data analysis was achieved by Graphpad Prism 5 software (GraphPad, San Diego, CA, USA). p Values were counted using a one-way analysis of variance (ANOVA). *(p < .05), **(p < .01) and ****(p < .001) stand for significant difference.

Results

CoCl₂ induced HK-2 cells hypoxia injury

Cell viability and apoptosis are two important aspects to detect cell growth. As presented in Figure 1A, cell viability was significantly decreased with the increasing of time duration especially when treatment time was longer than 12 h (p < .05, p < .01 or p < .001). 24 h was used in the following experiment as the treatment time. On the other hand, we found that cell apoptosis was significantly higher than CoCl₂ compared with control (p < .001, Figure 1B). Moreover, we examined the expression of apoptotic proteins. Results showed that CoCl₂ induced the expression of p53 (p < .01), Bax (p < .01) and cleaved-aspase-3 (p < .001) while inhibited Bcl-2 (p < .05) expression compared with control (Figure 1C).
Taken together, we found that CoCl₂ induced hypoxia injury successfully. Cocl₂ induced ROR upregulation

ROR was involved in p53 expression and regulated cell apoptosis [11,12], which might play vital roles in response to hypoxia injury. Therefore, we detected the expression of ROR in HK-2 cells. Result showed that the expression of ROR was upregulated by CoCl₂ treatment as relative to control (p < .05, Figure 2), which indicated that ROR might join the regulation network in hypoxia injury of HK-2 cells.

Overexpression of ROR reduced CoCl₂-induced HK-2 cell injury

In order to validate the roles of ROR, cells were transfected with pcROR to upregulated expression of ROR. The upregulation of ROR by transfection with pcROR indicated high transfection efficiency as shown in Figure 3A (p < .01). Then we detected ROR overexpression on cell growth factors. Interestingly, cell viability was enhanced (p < .05, Figure 3B), and apoptosis was inhibited (p < .05, Figure 3C) by ROR overexpression compared with NC. In addition, several apoptotic factors were analyzed using western blot. Results showed that p53 (p < .05), Bax (p < .05) and cleaved-Caspase-3 (p < .01) were downregulated while Bcl-2 (p < .05) was upregulated by ROR overexpression (Figure 3D,E). In the end, we determined the expression of hypoxia-inducible factor (HIF)-α and found that ROR overexpression increased the expression of HIF-α both in RNA and protein levels (Figure 3F). Taken together, we found that overexpression of ROR decreased CoCl₂-induced cell injury.

Silence of ROR promoted CoCl₂-induced cell injury

Similarly, we detected the silence of ROR. First, ROR was silenced by transfection with si-ROR (p < .01, Figure 4A). Then, the same series of experiments were performed in our study. Of the contrary, opposite results were induced by silence of ROR as evidence by inhibiting cell viability (p < .05,
Figure 4B), enhancing cell apoptosis \( (p < .05, \text{Figure 4C}) \). In addition, the apoptotic protein p53, Bax, cleaved-Caspase-3 and Bcl-2 were altered by ROR silence (Figure 4D,E). In the end, we found that silence of ROR decreased the expression of HIF-\( \alpha \) (Figure 4F). Above all, silence of ROR not only decreased the \( \text{CoCl}_2 \)-induced injury but also promoted the injury.

**Overexpression of ROR decreased miR-145 expression**

Previous study pointed out that lncRNA ROR functions via targeting miR-145 in hepatocellular cells [17]. Therefore, we detected the expression of miR-145 in \( \text{CoCl}_2 \)-induced injury in HK-2 cells. Interestingly, we found that \( \text{CoCl}_2 \) induced expression of miR-145 \( (p < .01) \) while ROR overexpression downregulated expression of miR-145 \( (p < .05, \text{Figure 5}) \), which indicated that miR-145 might be involved in the regulation network of ROR on \( \text{CoCl}_2 \)-induced hypoxia injury.

**ROR overexpression decreased \( \text{CoCl}_2 \)-induced injury via downregulation of miR-145**

To verify the roles of miR-145 in the network of ROR on cell injury, miR-145 mimic was transfected into cells to dysregulate expression of miR-145. The upregulation of miR-145 by transfection with miR-145 mimic \( (p < .01) \) suggested high transfection efficiency (Figure 6A). Then, further experiments were carried out to verify whether regulation work of ROR was related with miR-145. As expected, co-transfection with pcROR and miR-145 mimic decreased cell viability \( (p < .05, \text{Figure 6B}) \) and enhanced cell apoptosis \( (p < .05, \text{Figure 6C}) \) compared with NC in \( \text{CoCl}_2 \) treated HK-2 cells. In addition, miR-145 overexpression totally changed the expression of...
apoptotic proteins p53 (p < .05), Bcl-2 (p < .05), Bax (p < .05) and cleaved-Caspase-3 (p < .05, Figure 6D,E). Furthermore, miR-145 overexpression also decreased expression of HIF-α (p < .05, Figure 6F). From the results above, we can infer that the effects of ROR might through regulation of miR-145.

**ROR overexpression modulated extracellular regulated protein kinases (ERK) and mitogen-activated protein kinase (MAPK) signalling pathways through regulation of miR-145**

ERK and MAPK are signalling reported to be in hypoxia injury and also participated in OSAHS [18,19]. In our study, we found that CoCl2 decreased the phosphorylation of ERK (p < .05, Figure 7A) and increased the phosphorylation of p38MAPK (p < .001, Figure 7B) in HK-2 cells. ROR overexpression led to the opposite result led by CoCl2 (both p < .05, Figure 7A,B). Interestingly, another reversed trend was
induced by co-transfection with pcROR and miR-145 mimic which indicated that miR-145 overexpression impaired the effects of ROR overexpression (both *p* < .05, Figure 7A,B). Taken together, we concluded that ROR could affect CoCl₂-induced injury via ERK and MAPK signalling pathways.

**Discussion**

Clinical data pointed out that OSAHS, as one kind of common disease which influence the quality of life for the patients [20]. The current study was designed to explore further about the mechanism of OSAHS in order to search better treatment approaches for this disease. Our study investigated the roles of IncRNA ROR in CoCl₂-induced HK-2 cell injury. Furthermore, we also explored the network ROR did with the regulation of miR-145.

As aforementioned, OSAHS is a complex biological disease with multiple cellular and molecular regulation process. One important changed happened in this disease is hypoxia inflammatory injury [13,14]. In our study, we used CoCl₂ to stimulate HK-2 cells. Results with decreasing cell viability and increasing cell apoptosis even with altering the expression of...
apoptotic proteins indicated that CoCl₂ induced hypoxia injury in HK-2 cells. Similar with this treatment, CoCl₂ was often used to induce hypoxia injury [21].

Except the functions on cell viability and apoptosis, we also detected the effects of CoCl₂ on lncRNA ROR expression. Previous study has proved that the expression of ROR was enhanced in hypoxia treatment in hepatocellular cells [17]. Accordingly, our results showed that CoCl₂ increased the expression of ROR in HK-2 cells, which suggested that ROR might also work in HK-2 cells with hypoxia injury.

A series of experiments were performed to determine the function of ROR in HK-2 cells with hypoxia injury. Interestingly, our results demonstrated that overexpression of ROR promoted CoCl₂-stimulated HK-2 cells growth as evidenced by increasing cell viability and decreasing cell apoptosis. However, in H/R treated H9c2 cells, ROR overexpression blocked cell viability and promoted apoptosis [22]. Consider the hypoxia treatment situations are variants and also the cells are different, we could not make a conclusion about the roles of ROR just from the limited information we obtained.

Furthermore, we also detected the effects of ROR on apoptotic factors. As we have mentioned before, ROR was reported to functions in p53 expression [23]. Previous study was done in cancers but our study was HK-2 cells. Interestingly, our study showed that ROR overexpression decreased the accumulated level of p53, Bax and cleaved-Caspase-3 while upregulated expression of Bcl-2, which validated ROR inhibited cell apoptosis. Even though not so many previous studies were found in researching ROR on HK-2 cells, however, still several studies reported about the roles of ROR in cancers. For example, ROR enhanced proliferation, migration and chemoresistance of nasopharyngeal carcinoma [24]. Cited this reference, combined with our study, we inferred that ROR could regulate cell biological activities.

On the one hand, HIF-α which consist of an oxygen-sensitive α-subunit is an oxygen-dependent transcriptional activator closely connected with mammalian development [25]. In our study, ROR overexpression initiated its protective effects through HIF-α activation, similar like its roles in kidney injury [26]. On the other hand, silence of ROR underwent similar approaches from these series of experiments. Opposite was led by ROR silence as related to ROR overexpression, suggesting the same conclusion that ROR promoted HK-2 cells growth and development.

As we have mentioned data from former study that ROR has been functioning through miR-145 in hepatocellular cells [17]. From our study, we saw downregulation of miR-145 by...
ROR overexpression. Further studies demonstrated that miR-145 overexpression impaired the role of ROR overexpression in CoCl₂ stimulated HK-2 cells, suggesting that ROR overexpression achieved its functions through downregulation of miR-145. miR-145 was normally reported as a tumour suppressor inhibiting cell proliferation, migration, invasions in various kinds of cancers, such as human lung adenocarcinoma [27], prostate cancer [28], bladder cancer [29] and gastric cancer [30]. In addition, miR-145 was also popularly used in multiple injuries induced by different stimuli. For example, miR-145 alleviated lipopolysaccharides-induced inflammatory injury in human fibroblast-like synoviocyte MH7A cells [31]. By contrary, miR-145 was reported to promoted hypoxia-induced injury in H9c2 cells [32]. Combined previous studies and our own result, the roles of miR-145 various maybe because of different cell type and different treatments. However, to our best knowledge, this is the first time that the roles of ROR and miR-145 were investigated.

ERK and MAPK are two important signal pathways involved in hypoxia injury and importantly, these two pathways are also involved in OSAHS [18,19]. In our study, we found that CoCl₂ inactivated ERK while activated MAPK pathways while ROR overexpression reversed this trend shown by activation of ERK and inactivation of MAPK. Our study was consistent with the previous study that lncRNA ROR activated ERK pathway through in breast cancer [33]. Our study went further and unveiled one possible underlying in which miR-145 was involved in.

In conclusion, our study demonstrated that lncRNA ROR mitigated CoCl₂-induced hypoxia injury in HK-2 cells as evidenced by increasing cell viability, decreasing cell apoptosis and HIF-α expression. Moreover, our study explored further and found that the network of ROR in which miR-145 was involved in. ERK and MAPK were also connected in ROR response to hypoxia injury in HK-2 cells.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Agaba B, Jofah A. Facial phenotype in obstructive sleep apnea-hypopnea syndrome: a systematic review and meta-analysis. J Sleep Res. 2017;26:122–131.
[2] De Backer W. Obstructive sleep apnea/hypopnea syndrome. Panminerva Med. 2013;55:191–195.
[3] McDaid C, Griffin S, Weatherly H, et al. Continuous positive airway pressures for the treatment of obstructive sleep apnoea-hypopnoea syndrome: a systematic review and economic analysis. Health Technol Assess. 2009;13:i–iv, x–xiv, 1–119, 143–274.
[4] Jennum P, Riha RL. Epidemiology of sleep apnoea/hypopnoea syndrome and sleep-disordered breathing. Eur Respir J. 2009;33: 907–914.
[5] Basyuni S, Barabas M, Quinnell T. An update on mandibular advancement devices for the treatment of obstructive sleep apnoea hypopnoea syndrome. J Thorac Dis. 2018;10:548–556.
[6] Yao Q, Wu L, Li J, et al. Global prioritizing disease candidate lncRNAs via a multi-level composite network. Sci. Rep. 2017;7: 39516.
[7] Zhang J, Zhu Y, Wang R. Long noncoding RNAs in respiratory diseases. Histol Histopathol. 2018;33:747–756.
[8] Juan C, Wang Q, Mao Y, et al. Knockdown of LncRNA MALAT1 contributes to cell apoptosis via regulating NF-kB/CD80 axis in neonatal respiratory distress syndrome. Int J Biochem Cell Biol. 2018;104:138–148.
[9] Yang S, Chen J, Yu Y, et al. Long noncoding RNA ROR as a novel biomarker for progress and prognosis outcome in human cancer: a meta-analysis in the Asian population. CMAR. 2018;10:4641–4652.
[10] Weidle UH, Birzelle F, Kollmorgen G, et al. Long non-coding RNAs and their role in metastasis. CDP. 2017;14:143–160.
[11] Bauderlique-Le Roy H, Vennin C, Brocqaveille G, et al. Enrichment of human stem-like prostate cells with s-SHIP promoter activity uncovers a role in stemness for the long noncoding RNA H19. Stem Cells Dev. 2015;24:1252–1262.
[12] Yang Z, Tang Y, Lu H, et al. Long non-coding RNA reprogramming (lncRNA-ROR) regulates cell apoptosis and autophagy in chondrocytes. J Cell Biochem. 2018;119:8432–8440.
[13] Garvey JF, Taylor CT, McNicholas WT. Cardiovascular disease in obstructive sleep apnoea syndrome: the role of intermittent hypoxia and inflammation. Eur Respir J. 2009;33:1195–1205.
[14] Passali D, Corallo G, Yaremchuk S, et al. Oxidative stress in patients with obstructive sleep apnoea syndrome. Acta Otorhinolaryngol Ital. 2013;35:420–425.
[15] Liu Y, Zhang R, Ying K. Long noncoding RNAs: novel links in inflammation achieved its functions through downregulation of FSCN1. RNA. 2013;19:891–901.
[16] Lacedonia D, Scioscia G, Pia Palladino G, et al. MicroRNA expression profile during different conditions of hypoxia. Oncotarget. 2018;9:35114–35122.
[17] Takahashi K, Yan IK, Haga H, et al. Modulation of hypoxia-signaling pathways by extracellular linc-RoR. J Cell Sci. 2014;127:1585–1594.
[18] Ding W, Chen X, Li W, et al. Genistein protects genioglossus myoblast against hypoxia-induced injury through PI3K-Akt and ERK MAPK pathways. Sci Rep. 2017;7:5085.
[19] Retraction: genistein protects genioglossus myocyte against hypoxia-induced injury through PI3K-Akt and ERK MAPK pathways. J Cell Biochem. 2012;113:1809.
[20] Chen Q, Lin RJ, Hong X, et al. Treatment and prevention of inflammatory responses and oxidative stress in patients with obstructive sleep apnea hypopnea syndrome using Chinese herbal medicines. Exp Ther Med. 2016;12:1572–1578.
[21] Chu CY, Jin YT, Zhang W, et al. CA IX is upregulated in CoCl₂-induced hypoxia and associated with cell invasive potential and a poor prognosis of breast cancer. Int J Oncol. 2016;48:271–280.
[22] Zhang W, Li Y, Wang P. Long non-coding RNA-ROR aggravates myocardial ischemia/reperfusion injury. Braz J Med Biol Res. 2018; 51:e6555.
[23] Huarte M. The emerging role of lncRNAs in cancer. Nat Med. 2015;21:1253–1261.
[24] Li L, Gu M, You B, et al. Long non-coding RNA ROM promotes proliferation, migration and chemoresistance of nasopharyngeal carcinoma. Cancer Sci. 2016;107:1215–1222.
[25] Lee JW, Bae SH, Jeong JW, et al. Hypoxia-inducible factor (HIF-1)alpha: its protein stability and biological functions. Exp Mol Med. 2004;36:1–12.
[26] Zhang J, Liu A, Hou R, et al. Salidroside protects cardiomyocyte against hypoxia-induced death: a HIF-1alpha-activated and VEGF-mediated pathway. Eur J Pharmacol. 2009;607:6–14.
[27] Cho WC, Chow AS, Au JS. MI-R145 inhibits cell proliferation of human lung adenocarcinoma by targeting EGFR and NUDT1. RNA Biol. 2011;8:125–131.
[28] Fuse M, Nohata N, Kojima S, et al. Restoration of miR-145 expression suppresses cell proliferation, migration and invasion in prostate cancer by targeting FSCN1. Int J Oncol. 2011;38: 1093–1101.
[29] Chiyomaru T, Enokida H, Tatarano S, et al. miR-145 and miR-133a function as tumour suppressors and directly regulate FSCN1 expression in bladder cancer. Br J Cancer. 2010;102:883–891.
[30] Qiu T, Zhou X, Wang J, et al. MI-R145, miR-133a and miR-133b inhibit proliferation, migration, invasion and cell cycle progression.
via targeting transcription factor Sp1 in gastric cancer. FEBS Lett. 2014;588:1168–1177.

[31] Zhong F, Xu J, Yang X, et al. miR-145 eliminates lipopolysaccharides-induced inflammatory injury in human fibroblast-like synoviocyte MH7A cells. J Cell Biochem. 2018;119:10059–10066.

[32] Wang X, Zhang Y, Wang H, et al. MicroRNA-145 aggravates hypoxia-induced injury by targeting Rac1 in H9c2 cells. Cell Physiol Biochem. 2017;43:1974–1986.

[33] Peng WX, Huang JG, Yang L, et al. Linc-RoR promotes MAPK/ERK signaling and confers estrogen-independent growth of breast cancer. Mol Cancer. 2017;16:161.