Original Article HSA-miR-34a-5p regulates the SIRT1/TP53 axis in prostate cancer

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Abstract: SIRT1 is tightly associated with the progression of prostate cancer while the role of Hsa-miR-34a-5p in SIRT1-mediated prostate cancer is not fully understood. We have thoroughly mined the data from two databases, namely the Lipidemia and the cancer genome atlas (TCGA) and found that SIRT1 was highly expressed in human carcinoma tissues as compared to normal tissues, and patients with high SIRT1 expression level had a shorter survival time. The online tool "Gene-RADAR" was applied to investigate the interaction among SIRT1, the TP53 gene and miR-34a-5p. We found that SIRT1 was up-regulated in cancer tissues from patients diagnosed with prostate and castration-resistant prostate cancer when compared to healthy controls. Pearson analysis indicated a positive correlation between SIRT1 and miR-34a-5p, while data mining on the TargetScan database predicted the binding site between the two. An apoptosis assay of prostate cancer cells (PRAD) confirmed that the overexpression of miR-34a-5p inhibited paclitaxel-induced apoptosis and promoted cell proliferation. Cell cycle analysis verified that miR-34a-5p overexpression blocked PRAD cells in the G2/S phase of the cell cycle. Moreover, the Western blotting (WB) and quantitative PCR (qPCR) assays demonstrated that the overexpression of miR-34a-5p induced down-regulation of the SIRT-related proteins HIF2 α and PGC1 α , while on the contrary, it up-regulated the expression of two tumour suppressor genes, TP53 and VEGF. In conclusion, we have shown that miR-34a-5p is involved in the oncogenesis of PRAD cells via the SIRT1/TP53 axis.

Keywords: miR-34a-5p, prostate cancer, PRAD cells, SIRT1/TP53 axis, apoptosis, cell cycle, TP53 and VEGF

Introduction

The progression of prostate cancer depends on the androgen receptor (AR), and it seriously endangers men's lives. The 2019 Coffey-Holden Prostate Cancer Academy (CHPCA) meeting revealed that the next-generation sequencing technologies in genomics and transcriptomics are new promising diagnostic and therapeutic approaches for prostate cancer [1]. Regarding genomics, there is evidence that miRNAs play a vital role in the development of prostate cancer [2]. Their dysregulation influences various cell activities associated with prostate cancer. such as acceleration of cell proliferation, inhibition of cell apoptosis, promotion of epithelialmesenchymal transition and activation of the AR-mediated signaling pathway. Therefore, we regard it of great importance to investigate the function of miRNAs in the development of prostate cancer.

Hsa-miR-34a-5p is a p53-regulated tumor suppressor that modulates certain biologic functions such as p53-induced cell cycle arrest, apoptosis, senescence, and proliferation [3]. Reports have shown its involvement in the progression of various cancers [4, 5]. Furthermore, studies have indicated that the cell motility in bladder cancer was inhibited after the expression of the matrix metalloproteinase-2 (MMP-2) gene, which is also regulated by miR-34a-5p [4]. Additionally, hsa-miR-34a-5p intentionally downregulated the silent information regulator (SIRT1) in gastric cancer cells, thus modulating their multi-drug resistance [5]. Regardless of these data, the functions of hsa-miR-34a-5p in prostate cancer still need further investigation.

SIRT is an NAD-dependent deacetylase sirtuin and is a member of the class III group of histone deacetylases. It has an essential role in the regulation of energy metabolism and senescence. Mei et al. reported that the transport of SIRT1 triggered the mutation of TP53, which resulted in the metabolism of aerobic glycolysis and glutaminolysis [6]. In addition, SIRT3 and SIRT6 blocked RIPK3-related necroptosis and aggravated prostate cancer [7]. However, whether SIRT or hsa-miR-34a-5p was involved in prostate cancer still remains unknown.

Therefore, we have evaluated the regulation effect of hsa-miR-34a-5p on prostate cancer cells (PRAD) and investigated its underlying mechanisms. Our results suggest the regulatory effect of SIRT1 and miR-34a-5p and propose a new strategy against prostate cancer with the involvement of the SIRT1/TP53 axis regulated by hsa-miR-34a-5p.

Materials and methods

Cell culture

Prostate cancer cell lines, LN-CAP, PC-3 and DU145, were purchased from the Type Culture Collection of the Chinese Academy of Sciences (Shanghai, China). Cells were cultured in optimal conditions (37 °C and 5% of CO_2) in RPMI-1640 medium (Gibco, Logan, UT, USA), supplemented with 10% fetal bovine serum (FBS; Thermo, Waltham, MA, USA) and 1% Penicillin-Streptomycin Solution (Solarbio, China).

Bioinformatic analysis

The GEPIA2 database (http://gepia2.cancerpku.cn/#index) was explored to obtain the expression levels of SIRT1 mRNA in cancer tissues. Similarly, the TCGA database (http:// gepia2.cancer-pku.cn/#degenes) was used to find out the mRNA levels of SIRT1 in prostate cancer. The Kaplan-Meier survival curves were analyzed concerning the different levels of SIRT1 expression in prostate cancer via the GEPIA2 Survival Analysis (http://gepia2.cancerpku.cn/#survival). The interaction between SI-RT1, TP53 and miR-34a-5p were predicted by the Gene-RADAR tool (Genminix, China, https: //www.gcbi.com.cn/gclib/html/index). The correlation analysis was calculated via the GEPIA2 tool (http://gepia2.cancer-pku.cn/#correlation).

Cell transfection

For the prediction of the interaction between SIRT1 and miR-34a-5p, we employed the Tar-

getScan database (http://www.targetscan.org/ vert_71/). For the examination of the miR-34a-5p overexpression vector, the purified PCR product was cloned into the pCDH-CMV vector (System Biosciences) between the EcoRI and Notl sites. Constructs were confirmed by DNA sequencing. When the prostate cancer cells (LN-CAP, PC-3 and DU145) reached confluence up to 60-75% [8], the cells were transfected with miR-NC, miR-34a-5p mimic or miR-34a-5p inhibitor (Table 1) using the Lipofectamine® 2000 Transfection Reagent (Invitrogen). After 5 min, fresh media was added to the cells and they were incubated for 6 h. Then, the transfection solution was added and cells were used for the next assays after 48 h.

MTT assay

Initially, 50,000 cells/mL were seeded in a 96-well plate and were incubated with 20 μ L MTT solution (5 mg/mL, Dojindo, Shanghai, China) at 37°C for 3-4 h. Then, the culture medium was discarded, and 100 μ L of DMSO solution was added. After shaking, a Microliter plate reader (BioTek, Winooski, VT, USA) was applied to examine the optical density of each well at the wavelength of 570 nm.

Apoptosis detection

Cell apoptosis was verified by Annexin V-FITC/PI staining assay kit (Vazyme, Nanjing, China). After dilution of cells with a binding buffer (100 μ L), Annexin V was added to the cells and incubation for 10 min followed. Next, 300 μ L of binding buffer was added to resuspend the cells. Further, flow cytometry (FACS Calibur) was used to determine the fluorescence data. Results were analyzed by the FlowJo software (Treestar, Ashland, OR).

Cell cycle analysis

Cell cycle analysis was performed according to the method reported by Ma and colleagues [9]. A concentration of 1×10⁶ cells were fixed with 70% pre-chilled ethanol for 12 h in a freezer. After RNAase-free treatment, propidium iodide (PI) (Sigma) was added and then they were analyzed by Flow cytometry (Calibur; Becton Dickinson, Franklin Lakes). The FlowJo software (FlowJo LLC; Ashland) was again used to obtain the percentage of cell cycle distribution of the cell cycle.

	Forward	Reverse
miR-NC	5'-UUCUCCGAACGUGUCACGUTT-3'	5'-ACGUGACACGUUCGGAGAATT-3'
miR-34a-5p mimic	5'-CGGCAGGCAUUAGAGAUGAACAGCA-3'	5'-UGCUGUUCAUCUCUAAUGCCUGCCG-3'
miR-34a-5p inhibitor	5'-GTATGATTCACCACCTTCTC-3'	5'-CTCAACTGGTGTCGTGGAG-3'

Table 1. Primers sequences used cell transfection

Table 2. Primers sequences used for PCR

	Forward	Reverse
GAPDH	5'-TCCGTGGTCCACGAGAACT-3'	5'-GAAGCATTTGCGGTGGACGAT-3'
HIF-2α	5'-CTTGGAGGGTTTCATTGCTGTGGT-3'	5'-GTGAAGTCAAAGATGCTGTGTCCT-3'
SRIT1	5'-GCCTCATCTGCATTTTGATG-3'	5'-TCTGGCATGTCCCACTATCA-3'
U6	5'-CTCGCTTCGGCAGCACA-3'	5'-AACGCTTCACGAATTTGCGT-3'

Western blotting

Total protein (BCA protein assay kit, Thermo) was extracted with RIPA buffer (ThermoFisher Scientific). Proteins were then separated by SDS electrophoresis and transferred to a nitrocellulose filter membrane (NCF) (Millipore) via Western blotting, where the incubation was conducted in the presence of BSA (Millipore). Thereafter, the primary antibodies for detection of SRIT1, HIF-2 α , β -actin, VEGF and TP53 (1:1000; Cell Signaling Technology (CST)) as well as β -actin (1:2000, Santacruz) were incubated with the NCF membranes overnight. The secondary antibodies (Proteintech) were added then. The results were detected by an ECL kit (Amersham Pharmacia).

Real-time PCR

TRIzol reagent kit (Invitrogen, USA) was exploited for the total RNA extraction. RNA was converted into cDNA using a reverse transcriptase kit (Invitrogen). Using the ABI 7500 system SYBR Green (Thermo), the qRT-PCR process was conducted. The primer sequences are shown in **Table 2**. U6 and GAPDH were employed as internal controls and the $2^{-\Delta\Delta Ct}$ method enabled the calculation of the RNA levels.

Luciferase reporter assay

The potential binding sites between miR-34a-5p and the 3'-UTR of SIRT1 were detected and were cloned into the pGL3-basic vector. The pGL3 with pRL-TK vectors (Promega, Madison, USA) were respectively transfected into cells using Lipofectamine 2000 (Invitrogen, Carlsbad, USA). The Dual-Luciferase Reporter Assay System was employed to perform the luciferase reporter assays at 48 h after transfection.

Statistical analysis

SPSS 18.0 software was used for the statistical analyses of all data. The experimental data obtained from at least three independent experiments were displayed as MEAN \pm SD. The differences between the two groups were analyzed by the Student's t-test, while the differences among at least 3 groups were analyzed by one-way analysis of variance followed by Turkey post hoc test. Image J software was utilized to calculate the grey value in the Western blotting assays. GraphPad Prism 7 was applied for mapping and data analysis.

Results

A high expression of SIRT1 in prostate cancer tissues was obtained after bioinformatic analyses

We investigated the SIRT1 expression in different types of cancer tissues and normal tissues via the GEPIA2 database and the results showed SIRT1 overexpression in the cancer cells (Figure 1A). We further validated the role of SIRT1 in prostate cancer (PRAD) using the TCGA database. The findings demonstrated that the relative SIRT1 expression was elevated in cancer tissues of PRAD, especially in castration-resistant prostate cancer, when compared to normal tissue (Figure 1B, P<0.01). To better understand the relevance of SIRT1 expression in PRAD patients, we investigated the relationship of SIRT expression levels with the survival of the patients, and the results showed that the low expression of SIRT1 was



Figure 1. Up-regulation of SIRT1 in PRAD retrieved from various bioinformatic databases. A: SIRT1 was analyzed using the GEPIA2 database. The red lines represent the cancer tissues while the green ones - the normal tissues. B: Relative expression of SIRT1 in patients diagnosed with PRAD and patients with castration-resistant prostate cancer and healthy people (****P<0.0001, ####P<0.0001). C: Kaplan-Meier survival curves analyses of different concentrations of SIRT1 in PRAD (n=246, n=246, HR=2.8, P=0.12).

related to better overall survival time of PRAD patients as seen by the TCGA database (HR= 2.8, Log-rank P=0.12) (**Figure 1C**). The above

results suggest a possible relation between SIRT1 expression and the malignant progression of PRAD.

Correlation among the expression levels of SIRT1, TP53 and miR-34a-5p in prostate cancer

To explore the cellular metabolism of SIRT1 in PRAD, we used the Gene-Radar tool (Genminix, China, https://www.gcbi.com.cn/gclib/ html/index) to predict possible interactions among SIRT, TP53 and miR-34a-5p. Results are shown in Figure 2A. We discovered that SIRT1 and TP53 co-interacted with miR-34a-5p. Additionally, our results suggested that the SIRT1 level was positively associated with miR-34a-5p (Figure 2D, r=0.7850, P<0.05). We further examined the concentration of miR-34a-5p in patients with PRAD and patients with castration-resistant prostate cancer and compared it with normal tissues. As illustrated in Figure 2C, the expression pattern of miR-34a-5p was similar to that of SIRT1 (P<0.01). Furthermore, the miR-34a-5p overexpression inhibited the luciferase activity of the wild-type SIRT1 vector, but not the expression of the vector with the mutated SIRT1 (Figure 2E). Based on the data illustrated in Figure 2B, we observed a positive correlation between SIRT1 and TP53 (R=0.46, P<0.01). These findings verified the association of SIRT1 with the TP53 and miR-34a-5p.

miR-34a-5p reduced cell apoptosis and accelerated cell proliferation in prostate adenocarcinoma cells

To study the contribution of miR-34a-5p in the progression of PRAD, cell apoptosis and proliferation assays were conducted after transfecting prostate cancer cells with miR-NC, miR-34a-5p mimic or miR-34a-5p inhibitor. As shown in Figure 3A and 3B, the apoptosis rate was inhibited in the cells treated with a miR-34a-5p mimic (9.24%±1.89%), compared with the NC group (20.87%±2.12%), while the apoptosis rate was upregulated in cells transfected with the miR-34a-5p inhibitor (17.52%±1.63%) in DU145 cells. Similarly, the changing trend was the same in PC-3 cells (Figure 3C, 3D). The cell proliferation assay determined that the cell viability rate was significantly increased after transfection with a miR-34a-5p mimic in LN-CAP, DU145, PC-3 cells at 24 h, 48 h, 72 h (Figure 4A-C). Finally, the flow cytometry analyses determined the effect of miR-34a-5p on the cell cycle of prostate cancer cells (Figure 5). Interestingly, the obtained results showed a

significant accumulation of the cells in the G1 phase after treatment with miR-34a-5p inhibitor (G1/M=66.23 \pm 3.57% in LN-CAP, and 58.99 \pm 3.39% in PC-3 cells, respectively). On the contrary, the cells in the G1 phase were reduced in the miR-34a-5p mimic group (G1/M=31.32 \pm 6.02% in LN-CAP, and 40.22 \pm 3.77% in PC-3 cells, respectively), compared to the NC group (G1/M=49.21 \pm 5.67% in LN-CAP and 51.22 \pm 6.90% in PC-3). We also detected contradictory changes as cell cycle block in the G2/S phase. All the results indicated that miR-34a-5p may be important in the progression of PRAD by suppressing cell apoptosis and promoting cell proliferation.

miR-34a-5p is involved in the SIRT1/TP53 axis-related gene and protein expression

We further studied the molecular mechanism of the SIRT/TP53 axis by inducing a mutation in the 3'UTR of the SIRT1 gene. The WB assay verified the SIRT1 3'UTR mutation. Furthermore, our results based on the reported findings suggest that blocking the PRAD cells in the cell cycle could increase the expression of the TP53 protein compared with this of the control group (LN-CAP, PC-3), but on the other hand, could downregulate the expression of SIRT1, VEGF, HIF2 α and PGC1 α (**Figures 6** and **7**).

We further provided a schematic diagram of the miR-34a-5p/SIRT1/TP53 axis (**Figure 8**).

Discussion

In this study, we reported that SIRT1 expression levels are increased in prostate cancer (PRAD) and associated with poor prognosis. At the same time, miR-34a-5p reduced the apoptosis of PRAD cells and promoted their proliferation. Therefore, our results revealed the specific regulatory mechanism of miR-34a-5p in PRAD, suggesting that miR-34a-5p may become a potential therapeutic target for PRAD patients.

PRAD is a malignant disease that is linked with mutations in AR and genomic alterations in SPOP, c-Myc, and TP53 genes [10]. The molecular mechanism and metabolism in the initiation and progression of PRAD are complex. In that sense, abnormal oxygen and lactate metabolism are key points of various research on tumour oncogenesis and poor progression



Figure 2. Interaction of the SIRT-1 with TP53 gene via the miR-34a-5p. A: Prediction of the interaction between SIRT, TP53 gene and miR-34a-5p. B: Correlation analysis between SIRT and *TP53 gene* (R=0.46, P<0.01). C: Investigation of the miR-34a-5p expression in 3 groups of patients those with PRAD, with castration-resistant prostate cancer and normal (healthy patients) (****P<0.0001, ####P<0.0001). D: Analysis of the correlation between miR-34a-5p and SIRT1 (R=0.7850, P<0.05). E: Inquiry into the binding relationship between miR-34a-5p and SIRT-1 (***P<0.001, compared to miR-NC).



Figure 3. Suppression of cell apoptosis by MiR-34a-5p. A: Examination of the cell apoptosis in DU-145 cells; B: Apoptotic cell rate in DU-145 cells; C: Investigation of the cell apoptosis in PC-3 cells; D: Apoptotic cell rate in PC-3 cells; **P<0.01.



Figure 4. MiR-34a-5p inhibited cell viability. A: Cell viability in DU-145 cells; B: Cell viability in PC-3 cells; C: Cell viability in LN-CAP cells; compared to miR-34a-5p NC, *P<0.05, **P<0.01; compared to miR-34a-5p inhibitor, #P<0.05, ##P<0.01, ###P<0.001.

[11, 12]. Studies have indicated that lactate accumulation leads to anaerobic respiration and provides an environment for tumour growth [13, 14]. Li et al. reported that SIRT1 inhibited inflammation, apoptosis and autophagy of cells [15], while Ke and colleagues further confirmed that SIRT1 protected the mitochondrial metabolism in cells [16]. Additionally, emerging evidence suggested the association of SIRT1 with tumour proliferation, invasion and metastasis through the AMPK signaling pathway [17].

In this study, we explored the mRNA expression of SIRT1 in different types of cancer, such as ACC, BLCA, BRCA, LIHC, LUAD in the GEPIA2.0 database, which also included TGCA data [18]. In the literature, data revealed that SIRT1 was a target for DR [19]. Regardless of the SIRT1 expression in tumor progression, it may be a potential target for tumor progression.

To identify the role of SIRT1 in PRAD progression, we employed the TCGA database to ana-



Figure 5. MiR-34a-5p-accelerated cell proliferation. A: Representative cell cycle histograms of LN-CAP cells in the presence of miR-34a-5p NC (left); miR-34a-5p inhibitor (middle); and also in the presence of miR-34a-5p mimic (right); B: Comparison of the cell cycle proportion in LN-CAP cells in GO/G1, S and G2/M phases under the presence of miR-34a-5p NC, miR-34a-5p inhibitor and miR-34a-5p mimic; C: Representative cell cycles of PC-3 cells in the presence of miR-34a-5p NC (left); miR-34a-5p inhibitor (middle); and also in the presence of miR-34a-5p NC (left); miR-34a-5p inhibitor (middle); and also in the presence of miR-34a-5p mimic (right); D: Comparison of the cell cycle proportion in PC-3 cells in G0/G1, S and G2/M phases under the presence of miR-34a-5p NC, miR-34a-5p inhibitor and miR-34a-5p mimic; *P<0.05, **P<0.01.

lyze the differential mRNA expression levels of SIRT in TCGA normal and GTEx data of PRAD. The results indicated that SIRT1 expression in PRAD patients was higher than that in the normal ones. Moreover, a clinical trial also determined the expression of SIRT1 and SIRT family in the tissues of PRAD patients [20]. These findings were similar to ours, showing that the SIRT1 expression was higher in PRAD patients. The association of PRAD progression with autophagy, inflammation and oxidative stress has also been confirmed in previous studies [21, 22]. Therefore, in our studies, we were strictly focused on the interaction of SIRT1 and TP53. With the use of the CGBI online tool, we predicted the relationship between SIRT1 and TP53. Our findings revealed that SIRT and TP53 interacted with miR-34a-5p. Previous studies demonstrated that the miR-34a-5p targeted SIRT1 [23-25] to induce the accumulation of TNF- α and cycle arrest. Herein, with the use of the TGCA database, we investigated whether miR-34a-5p was positively correlated with Tp53 and SIRT1. Furthermore, we predicted the complementary sequences of miR-34a-5p and the 3'UTR of SIRT1 via the TargetScan database, which allowed us to establish a mutation in the 3'UTR region of the SIRT1 gene. This mutation was employed to detect the effect of SIRT1 on cell apoptosis, proliferation and cell cycle. The obtained results showed that SIRT1 and miR-34a-5p 3'UTR mutations slowed down the malignant progression of PRAD cells. Subsequently, the current study verified the key role of miR-34a-5p in the proliferation and cell cycle distribution of PRAD. Yet, the exact mechanism of action and the way it is bound to the SIRT1/TP53 axis has not been specified.

Finally, we detected the protein and gene expression of SIRT-1, HIF2α and PGC1α. Specifically, HIF2 α was suggested to have a close relationship with oxidative stress, whereas its abnormal expression could induce oxidative stress-related diseases and oncogenic mutations, such as p53 transcriptional activity [26]. Interestingly, the results indicated that SIRT1 3'UTR mutation may be involved in the hypoxic tumour environment and inhibit poor outcomes in tumours. Shih et al. reported that anaerobic respiration was induced as the outcome of the association of hypoxia with tumour cell growth [27]. Additionally, the interaction of SIRT1 with miR-34a-5p 3'UTR could maintain the activation of the SIRT1/TP53 axis and lead

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Figure 6. miR-34a-5p regulates the expression level of SIRT1/TP53 axis related protein. A: Western blotting bar of relevant protein in DU145 cells; B: Protein expression level in DU145 cells; C: Western blotting bar of relevant protein in LN-CAP cells; D: Protein expression level in LN-CAP cells; E: Western blotting bar of relevant protein in PC-3 cells; F: Protein expression level in PC-3 cells; **P<0.05, ***P<0.01, ***P<0.001.

to the malignant transformation of prostate cancer cells. Therefore, the regulatory mechanism of both SIRT1 and TP53 downstream of miR-34a-5p in PRAD presented a promising target for future studies. Finally, taking into account that miR-34a-5p exerted its function by targeting factors like VEGF, HIF-2 α and PGC-1 α as proposed already, further studies must be conducted to elucidate whether other tar-

gets contribute to the antitumor effect of miR-34a-5p inhibitor.

Conclusion

In conclusion, we found that SIRT1 was increased in PRAD tissues and was negatively associated with the prognosis of PRAD patients. Finally, we observed the involvement



Figure 7. miR-34a-5p was involved SIRT1/TP53 axis-related gene mRNA expression. A: mRNA expression level of HIF2 α in LN-CAP cells; B: mRNA expression level of HIF2 α in PC-3 cells; C: mRNA expression level of HIF2 α in DU-145 cells; D: mRNA expression level of PGC-1 α in LN-CAP cells; E: mRNA expression level of PGC-1 α in PC-3 cells; F: mRNA expression level of PGC-1 α in DU-145 cells; G: mRNA expression level of SIRT1 in LN-CAP cells; H: mRNA expression level of SIRT1 in PC-3 cells; H: mRNA expression level of SIRT1 in PC-3 cells; H: mRNA expression level of SIRT1 in PC-3 cells; H: mRNA expression level of SIRT1 in PC-3 cells; H: mRNA expression level of SIRT1 in DU-145 cells; H: mRNA expression level of SIRT1 in DU-145 cells; H: mRNA expression level of SIRT1 in DU-145 cells; H: mRNA expression level of SIRT1 in DU-145 cells; H: mRNA expression level of SIRT1 in DU-145 cells; H: mRNA expression level of SIRT1 in DU-145 cells; H: mRNA expression level of SIRT1 in DU-145 cells; H: mRNA expression level of SIRT1 in DU-145 cells; H: mRNA expression level of SIRT1 in DU-145 cells; H: mRNA expression level of SIRT1 in DU-145 cells; H: mRNA expression level of SIRT1 in DU-145 cells; H: mRNA expression level of SIRT1 in DU-145 cells; +**P<0.001.



Figure 8. Schematic diagram of the miR-34a-5p/SIRT1/TP53 axis.

of miR-34a-5p in the oncogenesis of PRAD cells via the SIRT1/TP53 axis.

Disclosure of conflict of interest

None.

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