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Biological Effect of The Interaction Between Mental Retardation Related Protein (FXR1P) and CMAS*

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Abstract Fragile X syndrome (FXS) is a genetic mental retardation disease, with incidence second only to trisomy 21 syndrome. Fragile X mental retardation protein(FMRP), is the causative factor of FXS and encoded by the Fragile X mental retardation1(*FMR1*) gene, which is widely expressed in cells of the nerve, muscle, and testes. Fragile X related protein 1 (FXR1P) is encoded by a homologous gene to *FMR1*——Fragile X related gene 1 (*FXR1*) and can interact with proteins and RNAs. Many illnesses were involved in the altered expression of *FXR1*. To understand the biological effect of the interaction between FXR1P and CMAS, we constructed a *FXR1* overexpression vector and investigated its expression in PC12 (the rat pheochromocytoma) cells and VSMC (vascular smooth muscle cell) and the effect of the overexpression on cell morphology and several cell processes related to CMP-N-acetylneuraminic acid synthetase (CMAS) activity. We demonstrate that the overexpression of *FXR1* gene can increase activity of CMAS in PC12 cells and provide a certain degree growth protection for that cells. Thus, it suggests FXR1P is a tissue-specific regulator to alter the concentration of GM1 in PC12 cells, but not in VSMC.

Key words FXR1P, CMAS, GM1, biological effect, PC12, VSMC
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Fragile X syndrome (FXS), also called Martin-Bell syndrome, is an inherited mental retardation disease associated with the low expression of Fragile X mental retardation 1(*FMR1*) gene and subsequently the reducing or missing of Fragile X mental retardation protein (FMRP)[1]. Fragile X related gene 1 (*FXR1*) is an autosomal homologue of the *FMR1* and locates at 3q28[2]. Fragile X related protein 1(FXR1P), encoded by *FXR1*, shares approximately 60% of its amino acid sequence with the N-terminal of FMRP that includes two KH domain, a RGG box, a Nuclear localization signal (NLS) and a Nuclear export signal (NES)[3].

The previous findings that FXR1P was normally expressed in the FXS patinents lacking FMRP indicated an independent function of FXR1P in development[4]. The change of FXR1P expression and the reduced stability of *FXR1* mRNA can result in facioscapulohumeral muscular dystrophy[5]. The animal study demonstrated that both *FMR1* and *FXR1* gene were involved in development of the eyes and neural crest. The reducing expression of these two genes can lead to the abnormal development of eyes and cranial cartilage, and the uncoordinate action in muscle and the growth abnormality of nerve tissue[6].

FXR1P is also expressed in mature oocyte and early vitro-fertilized embryos[7]. It was confirmed by vitro RNA immunoprecipitation assays in myocardial cells that FXR1P bound to *dsp*(desmoplakin) and *tln2*

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(talin2) mRNA and inhibited their translation , which two cognate proteins were localized to the desmosomes and costameres, respectively[8]. In addition, FXR1P can also bind to pre-miR-9 and pre-miR-124 and regulate the expression level of miR-124 by effecting the forming [9]. The compartmentalized AGO2-FXR1-isoform-a complex was reported to be selectively contributed to microRNA-mediated upregulation of some specific mRNAs transcription in quiescent (G0) mammalian cells and immature *Xenopus laevis* oocytes[10].

We have previously screened some proteins by yeast-2-hybrids and identified some protein that can interact with FXR1P such as CMP-N-acetylneuraminic acid synthetase (CMAS), *Homo sapiens* ferritin, heavy polypeptide 1 (FTH1)[11].

CMAS is an enzyme that can catalyze the activation of sialic, which is involved in the sialoglycoconjugate synethsis in the membrane [12]. In this study, we performed an *in vitro* study of FXR1 expression in two cell lines, the PC12 (rat pheochromocytoma) cells and VSMC (the vascular smooth muscle cell), using recombinant vector and empty vector, the wild-type cells as control, and investigated the effect of overexpression of FXR1 on cell morphology and several cell events mediated by CMAS such as the concentration of GM1, the total ATPase activity and the apoptosis rate. We want to determine the biological effect of the interaction between FXR1P and CMAS using these methods.

1 Materials and methods

1.1 Strains and cell lines

The *Escherichia coli* (*E. coli*) strains, DH5α (supE44ΔlacU169 hsdR17 recA1 endA1 gyrA96 thi-1relA1), was cultured in LB medium (1% tryptone, 0.5% yeast extract, 1% NaCl, pH 7.0) at 37℃ . Two cell lines, PC12 and VSMC, were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum in a humidified 5% CO_2 incubator at 37℃ .

1.2 Plasmid

The full open reading frame of the human *FXR1* gene was inserted into the pcDNA3.1 (-) vector to generate recombinant vector pcDNA3.1 (-)/*FXR1*. Then that was transfected into PC12 and VSMC cells.

1.3 Cell transfection

When the cells reached 80% confluence, they were placed into 6-well plates with basal DMEM without fetal calf serum or antibiotics and cotransfected with the mammalian expression plasmids pcDNA3.1 (-)/*FXR1* or pcDNA3.1 (-) using Lipofectamine 2000, the normal cell as control. Then, the transfected cells were incubated about 5 h, after which the medium was replaced with complete DMEM containing 10% fetal calf serum. At 48 h after transfection, the cells were harvested.

1.4 Western blot

Harvested cells were lysed by strengthen lysate. BCA Protein Assay Kit (Beyotime) was used to quantify the protein as manufacturer. Subpackage protein, according to 50 μg total protein, prepared to work as sample, and add 5×SDS-PAGE loading buffer and run on 120V. The primary antibody and secondary antibody was RIPAb+™ FXR1 and anti-GAPDH, respectively.

1.5 Observation of cell morphology

Cells in the logarithmic phase were collected on batch culture plate, and cultured in a humidified 5% CO_2 incubator at 37℃ for 24～48 h. Then, cells were fixed with paraformaldehyde and stained with DAPI (KeyGEN BioTECH). The observation was performed under confocal laser scanning microscope (Nikon).

1.6 Assay of concentration of GM1

ELISA assay was performed by the Human anti-ganglioside antibody (GM1) ELISA Kit (Biocalvin BioTech Co. Ltd) as manufacturer.

1.7 Assay of activity of total ATPase

Digest the cultured cell to acquire cell precipitation. Then the precipitation were treated with iso-osmia physiological saline. Transfer the suspension to 2 ml glass homogenate tube in order to get cell suspending liquid which will be detected the total activity of ATPase by the super microscale ATPase test Kit.

1.8 Assay of aopotosis rate

Prepare the analyte sample to single cell suspension and fixed it with 70% cold ethanol in oder to suspend the cell. Then deliver the sample to Junhong Bio (Changsha) Co. Ltd to detect the apoptosis rate.

2 Results

2.1 Construction and identification of pcDNA3.1(-)/FXR1

In order to study the biological effect of the interaction between FXR1P and CMAS, we designed a pair of primers to amplify the full open reading frame

of human *FXR1* about 1 900 bp by PCR, then inserted this amplified fragment into the pcDNA3.1(-) plasmid to obtain a recombinant pcDNA3.1(-)/*FXR1* vector. Then, the recombinant vector pcDNA3.1(-)/*FXR1* was confirmed to have full coding sequence of human *FXR1* by direct sequencing and restriction endonuclease analysis(*Xho* Ⅰ+*Eco*R Ⅰ).

2.2 Detection of the recombinant vector pcDNA3.1(-)/FXR1 transfection by Western blot

We selected two cell lines, PC12 (Rat pheochromocytoma) and VSMC (vasular smooth muscle cell) as the target cells transfected with recombinant vector pcDNA3.1(-)/*FXR1* due to higher expression of *FXR1* in the neural and muscle cells. The transfection efficiency was determined by the expression amount of FXR1. To determine relative level of FXR1 expression after transfection we designed two negative control groups, the vector-free and the empty vector, besides the group with *FXR1* vector transfection. Western blotting analysis showed that *FXR1* expression after transfection was increased by 36% in PC12 cells (Figure 1) and by 97.1% in VSMCs (Figure 2) against the vector-free group, whereas there was no significant alteration of *FXR1* expression between the empty vector and normal groups. The results revealed that two cell lines presented an over-expression of *FXR1* after *FXR1* vector transfected.

2.3 Overexpression of *FXR1* alters the morphology of VSMC but not PC12 cells

To evaluate the effect of over expression of FXR1 on the cell morphology, we compared the cell morphology by confocal laser scanning microscope among three groups. The results showed that the cell morphology has no significant difference in the PC12 cells among the three groups(Figure 3). However, the VSMC cells transfected with the recombinant vector pcDNA3.1(-)/*FXR1* exhibited an irregular shape rather than the fusiform which is the morphology of normal cells and others transfected with the empty vector (Figure 4). This indicated that overexpression of *FXR1* can alter cell morphology of the VSMC, but not that of PC12 cells.

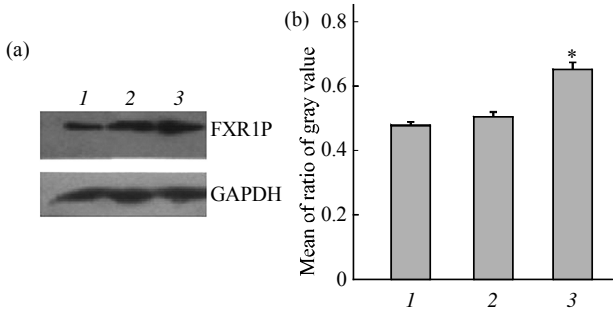

Fig. 1 Transfection efficiency of recombinant vector pcDNA3.1(-)/*FXR1* in PC12 cells by Western blot

(a) Western blotting of pcDNA3.1(-)/*FXR1* in PC12 cells. (b) Gray value analysis of Western blotting. *1*: Normal group; *2*: Empty vector group; *3*: Overexpression of *FXR1* group. *Compared with normal cell group, $P < 0.05$, n=3.

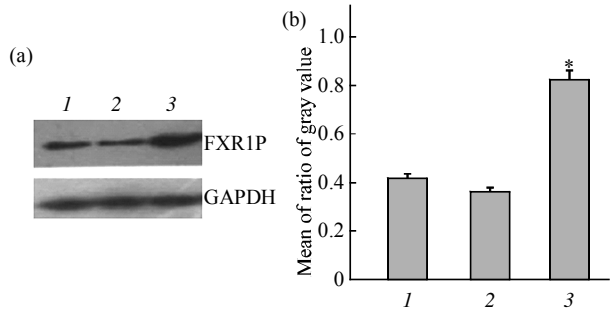

Fig. 2 Transfection efficiency of recombinant vector pcDNA3.1(-)/*FXR1* in VSMC by Western blot

(a) Western blotting of pcDNA3.1(-)/*FXR1* in VSMC. (b) Gray value analysis of Western blotting. *1*: Normal group; *2*: Empty vector group; *3*: Overexpression of *FXR1* group. *Compared with normal cell group, $P < 0.05$, n=3.

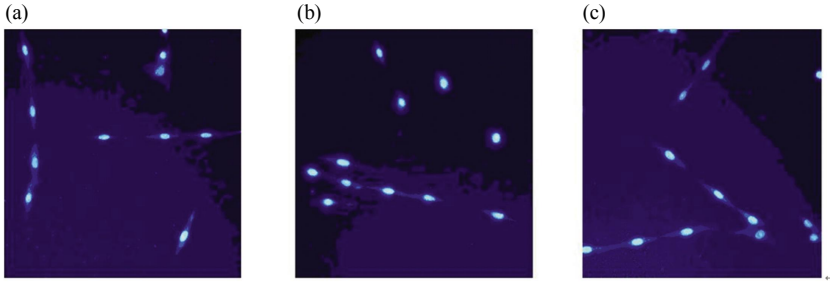

Fig. 3 Effect of overexpression *FXR1* on the morphology of PC12 cell

(a) Normal group. (b) Empty vector group. (c) Recombinant vector group. ×200

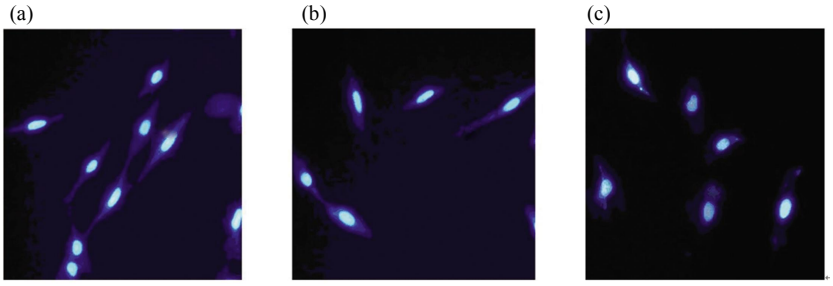

Fig. 4 Effect of overexpression *FXR1* on the morphology of VSMC

(a) Normal group. (b) Empty vector group. (c) Recombinant vector group. ×200

2.4 Overexpression of *FXR1* increases the concentration of GM1 in PC12 cells but not in VSMC

Our previous study has demonstrated the *in vitro* interaction of FXR1P with CMAS by yeast-2-hybirds. And CMAS can catalyze the synthesis of CMP-sialic acid from sialic acid and CTP. CMP-sialic acid is an active form of sialic and the raw material of ganglioside(GM) synthesis. Consequently, the relative amount of the sialic acid transferring into GM1 in cells was used as an indirect indicator for CMAS activity. To estimate the effect of overexpression of FXR1 on CMAS activity, we measured the concentration of GM1 in two cell lines among three groups. ELISA assay showed that the concentration of GM1 appeared a significant increase in PC12 cells transfected with recombinant vector (71.8%), but not in those PC12 cells with the empty vector, compared with the normal group (Figure 5a, Table 1). However, there were no obvious difference at GM1 concentration in VSMC among all three groups. This result suggested that overexpression of *FXR1* can increase the concentration of GM1 in PC12 cells and promote CMAS activity, but not in VSMC cells (Figure 5b, Table 1).

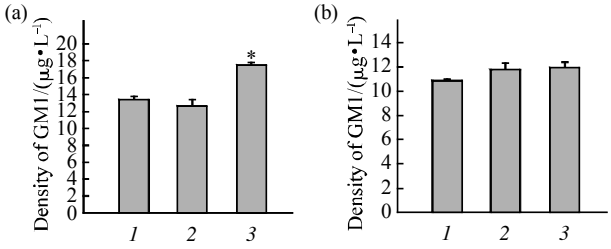

Fig. 5 Effect of overexpression *FXR1* on the concentration of GM1

(a) The concentration of GM1 in PC12. (b) The concentration of GM1 in VSMC. *Compared with normal cell group, $P < 0.05$, n=4. *1*: Normal group; *2*: Empty vector group; *3*: Overexpression of *FXR1* group.

Table 1 GM1 concentration in two cell lines transfected with or without FXR1

	Normal group	Empty vector group	Overexpression of *FXR1* group
PC12	13.445±0.384	12.675±0.787	17.483±0.342*
VSMC	10.838±0.082	11.756±0.531	11.928±0.441

*Compared with normal cell group, $P < 0.05$，n=4.

2.5 Overexpression of *FXR1* increases total ATPase activity in PC12 cells but not in VSMC

The concentration of GM1 in cells was evidenced to influence the activity of Na^+K^+-ATPase and $Ca^{2+}Mg^{2+}$-ATPase in cells [13]. To further confirm that overexpression of *FXR1* leading to the rise of GM1 level, we assayed total ATPase activity. The results showed that the PC12 cells transfected with recombinant vector had 75.3% more Na^+K^+-ATPase activity (Figure 6a, Table 2) and 52.5% more $Ca^{2+}Mg^{2+}$-ATPase activity (Figure 7a, Table 3) than those normal or empty vector cells did. On the other

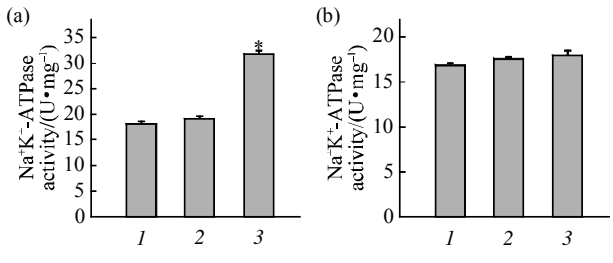

Fig. 6 Effect of overexpression *FXR1* on Na^+K^+-ATPase activity

(a) The Na^+K^+-ATPase activity in PC12. (b) The Na^+K^+-ATPase activity in VSMC. *Compared with normal cell group, $P < 0.05$, n=3. *1*: Normal group; *2*: Empty vector group; *3*: Overexpression of *FXR1* group.

hand, in VSMC cell, Na^+K^+-ATPase or $Ca^{2+}Mg^{2+}$-ATPase activity (Figure 6b, 7b, Table 2, 3) has no significant variations among the three groups.

Table 2　Assay of Na^+K^+-ATPase activity

	Normal group	Empty vector group	Overexpression of *FXR1* group
PC12	18.179±0.590	19.259±0.336	31.864±0.613*
VSMC	16.903±0.238	17.574±0.170	17.998±0.532

*Compared with normal cell group, $P < 0.05$，n=3.

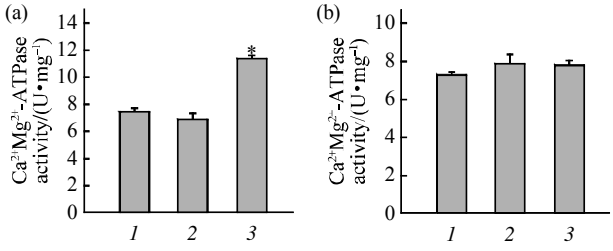

Fig. 7　Effect of overexpression *FXR1* on the $Ca^{2+}Mg^{2+}$-ATPase activity

(a) $Ca^{2+}Mg^{2+}$-ATPase activity in PC12. (b) $Ca^{2+}Mg^{2+}$-ATPase activity in VSMC. *Compared with normal cell group, $P < 0.05$，n=3. *1*: Normal group; *2*: Empty vector group; *3*: Overexpression of *FXR1* group.

Table 3　Assay of $Ca^{2+}Mg^{2+}$-ATPase activity

	Normal group	Empty vector group	Overexpression of *FXR1* group
PC12	7.489±0.266	6.915±0.320	11.418±0.552*
VSMC	7.307±0.090	7.889±0.455	7.801±0.229

*Compared with normal cell group, $P < 0.05$，n=3.

2.6　Overexpression of *FXR1* prevent from apoptosis in PC12 cells but not in VSMC

GM1 was previously found to protect cells from apoptosis [14]. We compared the apoptosis rate among the three groups. In PC12 cells, a significant reduction of the apoptosis rate appeared in the *FXR1*-transfected group, which the reduced percentage was 72.7% and 76.5% compared to the normal group and empty vector group, respectively (Figure 8, Table 4). However, there were no significant differences of the apoptosis rate in VSMC among the three groups (Figure 9, Table 4). This demonstrated that overexpression of *FXR1* can decrease the apoptosis rate in PC12 cell but not in VSMC.

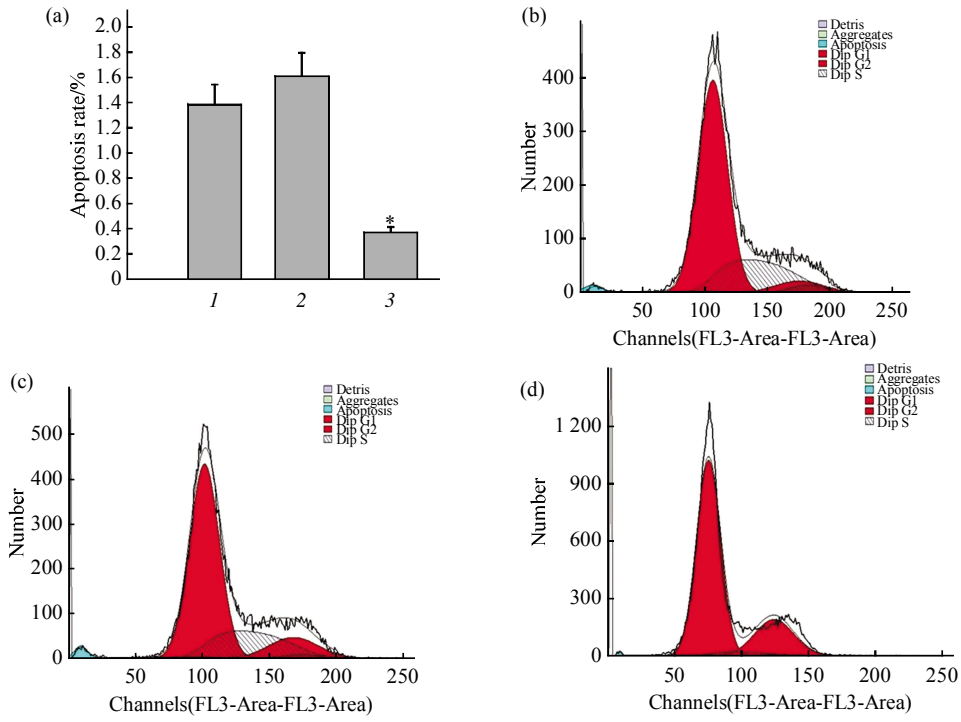

Fig. 8　Effects of overexpression *FXR1* on the apoptosis rate of PC12 cells

(a) Difference of apoptosis rate of all group PC12 cells. *1*: Normal group; *2*: Empty vector group; *3*: Overexpression of *FXR1* group. (b) Normal group. (c) Empty vector group. (d) Overexpression of *FXR1* group. *Compared with normal cell group, $P < 0.05$，n=3.

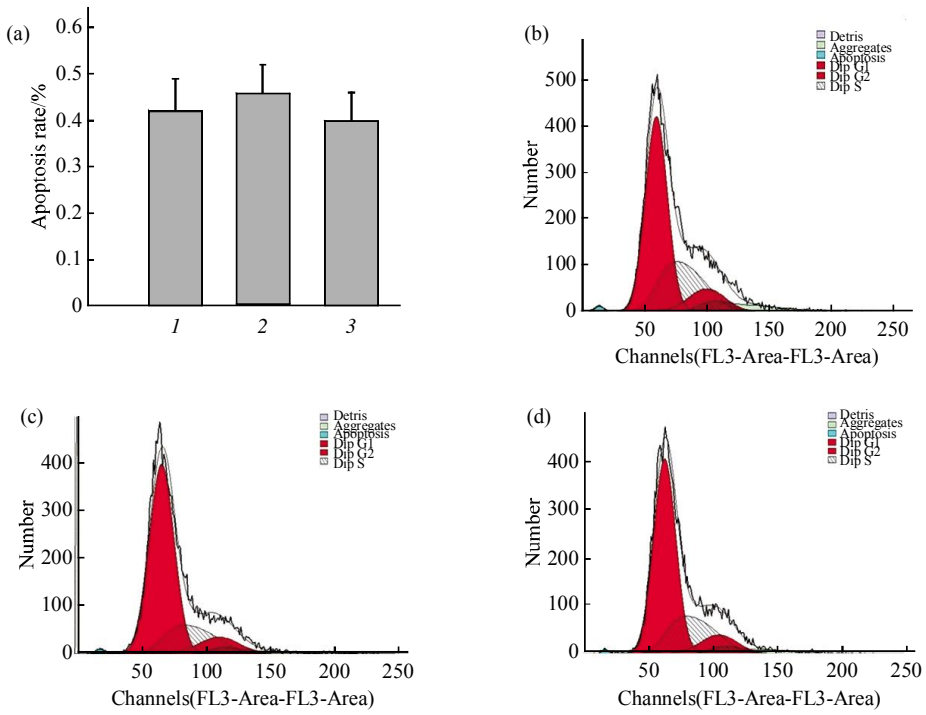

Fig. 9 Effect of overexpression *FXR1* on the apoptosis rate of VSMC

(a) Difference of apoptosis rate of all group VSMC. *1*: Normal group; *2*: Empty vector group; *3*: Overexpression of *FXR1* group. (b) Normal group. (c) Empty vector group. (d) Overexpression of *FXR1* group.

Table 4 Assay of apoptosis rate

%

	Normal group	Empty vector group	Overexpression of *FXR1* group
PC12	1.39±0.16	1.62±0.18	0.38±0.04*
VSMC	0.42±0.07	0.46±0.06	0.40±0.06

*Compared with normal cell group, $P < 0.05$, n=3.

3 Discussion

The discovery of the mental retardation related genes *FXR1* and *FXR2* spurred a large number of studies, but what is the role of them in growth and development of human, especially in FXS remains unclear. Recently, by co-IP and subcellular co-localization assasys, we have found FXR1P can interact with CMAS and FTH1 *in vitro*[11].

CMAS is an enzyme and widely exists in prokaryotes and eukaryotes. It activates sialic acid, and further generates various ganglioside Monosialote- tra hexosyl ganglioside-GM1, which maintains the activity of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase of cells membrane.

In this investigation we demonstrate that overexpression of *FXR1* increases the concentration of GM1 in PC12, which was executed by promoting the CMAS activity. Surprisingly, this effect was limited to PC12 cells, and the GM1 concentration in VSMC remained the same regardless of *FXR1* overexpression. PC12 cells are rat adrenal pheochromocytoma cell line originating from the neural crest at embryonic development and is commonly used as nerve cells in the research of interest. On the other hand, VSMC are rat vascular smooth muscle cell. The function of ganglioside in neurogenesis, growth and differentiation is a special phenomenon in nerve system, thus we supposed regulation of GM1 levels is tissue-specific.

GM1 inhibits apoptosis of nerve cells through multiple pathways such as the inhibition of Capase3, the activation of phosphatidylinositol kinase and sphingosine kinase[14–15], promotion of Bcl-2 expression and inhibition of Bax expression. Overexpression of Bax results in the apoptosis, whereas overexpression of Bcl-2 inhibits apoptosis [16–17]. In this study, we

demonstrate that overexpression of *FXR1* decreases the apoptosis rate in PC12 cells through increasing the GM1 level. However, the effects of anti-oxidation and removal of free radicals should not be ignored. Further study is needed in morphology and the concentration and degradation of DNA.

In the PC12 cell, overexpression of *FXR1* enhanced the concentration of GM, increased the activity of Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase, and decreased the apoptosis rate. But in VSMC the same changes had not been detected. These results suggest that overexpression of *FXR1* is able to reinforce the activity of CMAS which has been confirmed has interaction with FXR1P in PC12, and then raise the concentration of GM1 so as to protect the PC12 cell from injury. The absence of these change and the irregular cell morphology of VSMC due to FXR1 overexpression suggest that the protective elements were not conferred onto VMSC cells.

We study the biological effects based on the interaction between FXR1P and CMAS by overexpressing the *FXR1* gene in PC12 and VSMC cell. However, FXR1P is an RNA-binding protein. To identify which the target mRNA bind to FXR1P and what the regulation network is at work will become the research priorities for us.

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智力低下相关蛋白(FXR1P)与 CMAS 相互作用的生物学效应研究 *

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摘要　脆性 X 综合征(FXS)是一种遗传性智力低下疾病，其发病率仅次于 21 三体综合征．脆性 X 智力低下蛋白(FMRP)是 FXS 的关键性致病因子，该蛋白由脆性 X 智力低下基因 1(*FMR1*)编码所得．*FMR1* 在神经肌肉和睾丸组织中广泛表达．脆性 X 相关蛋白 1(FXR1P)则是由 *FMR1* 的同源基因脆性 X 相关基因 1(*FXR1*)编码所得，并且与蛋白质和 RNAs 之间存在着相互作用．许多疾病都涉及到 *FXR1* 表达的改变．为了了解 FXR1P 与 CMAS(胞嘧啶单核苷酸 -N- 乙酰神经氨酸合成酶)相互作用所产生的的生物学效应，我们构建了 *FXR1* 的过表达载体，并观察其在 PC12 细胞(大鼠鼠肾上腺嗜铬细胞瘤细胞)和 VSMC (血管平滑肌细胞)中的表达以及继而对于细胞形态和 CMAS 活性相关的许多细胞指标的效应．我们证实，*FXR1* 基因的过表达可以提高 PC12 细胞中 CMAS 的活性，并对于该类细胞的生长提供一定程度的保护作用．PC12 细胞是一种较为常见的用于研究神经系统疾病的细胞系．结论：我们推测 FXR1P 是一个组织特异调节因子，可以改变 PC12 细胞而非 VSMC 细胞中神经节苷酯(GM1)的浓度．

关键词　FXR1P，CMAS，GM1，生物学效应，PC12 细胞，VSMC
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