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Article

Dysregulation of the MEG3–ATF4 Axis in ST-Segment Elevation Myocardial Infarction: A Proof-of-Concept Study

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Abstract

Background/Objectives: Cardiovascular disease is the leading cause of morbidity and mortality worldwide, of which the myocardial Infarction is the most prevalent. However, the underlying pathophysiological mechanisms remain incompletely understood, but are tightly regulated by several cellular mechanisms, including long-non-coding. This study aimed to determine if *MEG3* and *ATF4* are involved in this pathology. **Methods:** A cross-section study was conducted at the Instituto Nacional de Cardiología Ignacio Chávez, patients with first time diagnosis STEMI and hemodynamic stability were categorized into with and without major adverse cardiovascular events, the most important clinical and biochemical parameters were collected, which were analyzed and subsequently correlated with *MEG3* and *ATF4*. **Results:** Forty-two patients with a median age of 54 years (86% men) were included and classified with and without MACE. The expression of *MEG3* in MACE group and No MACE (0.8974, 0.4186–1.4131 vs. 1.2259, 0.5516–2.3964; $p = 0.0342$), and *ATF4* in MACE group and No MACE (2.8950, 0.7559–4.3287 vs. 2.3498, 1.0821–3.6903; $p = 0.0396$), ROC curve *MEG3* showed an AUC of 0.6490 (0.4760 to 0.8221; $p = 0.0924$), in contrast *ATF4* demonstrated an AUC of 0.7127 (0.5862 to 0.8393; $p = 0.0107$). Finally, correlation analyses revealed *MEG3* was associated with CK-MB ($r = 0.3978$, 0.0630 to 0.6520; $p = 0.0219$), and *ATF4* was correlated cTnT ($r = 0.3328$, 0.0284 to 0.5810; $p = 0.0335$) and with LVEF ($r = -0.4283$, -0.6503 to -0.1390 ; $p = 0.0052$). **Conclusions:** The dysregulation of *MEG3* and transcription factor *ATF4* are involved in pathophysiological mechanisms.

Keywords: *MEG3-ATF4* Axis; cardiovascular disease; ischemia-reperfusion; long non-coding RNAs

1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. In Mexico, coronary artery disease (CAD) is the primary cause of death among the general population [1]. The occlusion of coronary arteries results in irreversible myocardial injury, and timely recognition of this event is fundamental to initiate reperfusion therapies for myocardial infarction (MI). These interventions aim to salvage viable myocardium, preserve systolic cardiac function, and limit infarct

size. However, ischemia-reperfusion (I/R) injury commonly occurs during these procedures, and the underlying pathophysiological mechanisms remain incompletely understood [2]. Despite the use of reperfusion strategies, no effective therapy currently exists to prevent myocardial I/R injury. Without further medical innovation, it is estimated that by 2030, more than 23.6 million people will die annually from CVD [3]. In Mexico, only 5 out of 10 patients with ST-segment elevation myocardial infarction (STEMI) have access to reperfusion therapy [4].

Long non-coding RNAs (lncRNAs), defined as RNA transcripts longer than 200 nucleotides, play crucial regulatory roles at the epigenetic, transcriptional, and post-transcriptional levels. This class of non-coding RNAs has been increasingly associated with the pathophysiology of CVD, including MI. The distinct expression profiles of lncRNAs in various cardiovascular conditions offer significant promise as both biomarkers and therapeutic targets [5]. Among these, the lncRNA maternally expressed gene 3 (*MEG3*), an imprinted gene within the *DLK-*MEG3** locus located on chromosome 14q32.3, is highly conserved and enriched in human cardiac tissue [6]. *MEG3* regulates multiple biological processes and is particularly relevant in cardiac fibroblasts, where it promotes fibrosis, making it the most specific lncRNA marker for this cell type [7]. Furthermore, *MEG3* expression induces cardiomyocyte apoptosis and is significantly upregulated in the left ventricle after MI compared with healthy cardiac tissue [8].

MEG3 also functions as a competitive endogenous RNA (ceRNA), sequestering microRNAs to regulate downstream mRNA expression. One of its key target is microRNA-214 (miR-214), which it directly binds and inhibits. miR-214, in turn, targets activating transcription factor 4 (ATF4), a key effector component of the endoplasmic reticulum (ER) stress pathway. ATF4 controls the expression of genes involved in oxidative stress, inflammation, and apoptosis [9]. Importantly, ATF4 has been shown to mitigate myocardial ER stress and reduce apoptosis during I/R injury [10].

This study aims to investigate the relationship between STEMI and the expression levels of *MEG3* and *ATF4* in STEMI patients using reverse transcription quantitative polymerase chain reaction (RT-qPCR).

2. Results

2.1. Clinical Characteristics of Patients at Hospital Admission

During the study period, 42 patients with STEMI were hospitalized, the median age of STEMI patients was 54 years (49–58), and the majority were male (86%). The median length of hospital stay was 5 days (3–7). Additionally, blood samples were obtained from 24 healthy controls (83% male; median age 55 years, 51–60).

The most relevant clinical and demographic characteristics of STEMI patients included a high prevalence of active smoking (72%) and comorbidities such as diabetes mellitus (39%) and hypertension (37%). Laboratory findings at admission revealed leukocytosis and elevated levels of N-terminal pro b-type natriuretic peptide (NT-proBNP), cardiac troponin T (cTnT), creatine kinase-MB (CK-MB), and high-sensitivity C-reactive protein (hsCRP) (Table 1).

Table 1. Patient characteristics at hospital admission.

	All patients (n= 42)	MACE (n= 22)	No MACE (n= 20)	P-value
Age in years	54 (49–58)	53 (48–57)	54 (50–59)	0.494
Male sex	37 (86)	18 (81)	19 (95)	0.346
BMI	27.3 (25.8–29.3)	27.3 (26.0–28.2)	27.4 (25.2–27.4.2)	0.954
Current smoking	31 (72)	14 (63)	17 (85)	0.165
Comorbid conditions				
Diabetes mellitus (%)	17 (39)	16 (27)	11 (85)	0.115
Systemic hypertension (%)	16 (37)	9 (40)	7 (35)	0.758
Dyslipidemia (%)	110 (23)	13 (13)	17 (35)	0.152

COPD (%)	0	0	0	>0.999
Main clinical data				
Temperature, °Celsius	36 (36–36)	36 (36–36)	136 (36–36)	0.842
Respiratory rate, breaths/min	18(16–20)	18 (16–19)	20 (16–20)	0.195
Heart rate, beats/min	75(69–90)	77 (70–89)	75 (66–92)	0.808
SBP, mmHg	131(115–149)	129 (110–150)	133 (126–146)	0.437
DBP, mmHg	80 (93–70)	80 (70–96)	81 (75–93)	0.862
O2 saturation (%) at room air	95 (92–95)	95 (95–97)	93 (91–94)	0.007
Laboratory values				
Leukocytes, 1x103 perm3	10.44 (8.75–14.45)	15,5 (15.8–14.05)	9.9 (8.9–11.8)	0.164
Hemoglobin, g/dl	15.5 (14.50–16.50)	12.2 (8.6–15.6)	15.9 (14.9–16.7)	0.188
Albumin, g/dl	4.0 (3.68–4.25)	4.0 (3.7–4,2)	4.1 (3.6–4.2)	0.335
cTnT, ng/ml	2947 (1926–6217)	2843 (1386–6217)	3196 (2241–5983)	0.220
NT-proBNP, ng/ml	1911 (1188–3691)	3069 (1731–4287)	1369 (841–2062)	0.005
Creatine kinase MB, U/l	52 (9.2–117.2)	19.5 (5.6–97.1)	85 (28–173)	0.171
Creatine kinase, U/l	883 (332–1611)	967 (184–1463)	849 (444–1689)	0.352
D-dimer, ng/ml	0.4 (0.2–0.5)	0.4 (0.2–0.5)	0.3 (0.2–0.7)	0.273
Fibrinogen, mg/dl	4.8 (3.2–6.1)	5.5 (3.7–4.2)	3.3 (3.0–5.7)	0.105
C-reactive protein, mg/l	15.4 (6.1–86.5)	14.7 (5.6–84.6)	40.9 (8.7–82.9)	0.861
Days of hospital stay	5 (3–7)	5 (4–8)	4 (3–5)	0.057

Data are presented as mean ± standard deviation unless otherwise specified. Significance P values are in bold. BMI: body mass index; COPD: chronic obstructive pulmonary disease.

2.2. Laboratory Data

The expression of MEG3 was significantly lower in STEMI patients compared to healthy controls (1.0489, 0.0489–2.0054 vs. 2.3849, 1.9950–2.5652; p = 0.048). In contrast, ATF4 expression was significantly higher in STEMI patients (2.4032, 1.0000–4.3019 vs. 2.2407, 1.6362–3.1327; p = 0.0070) (Figure 1).

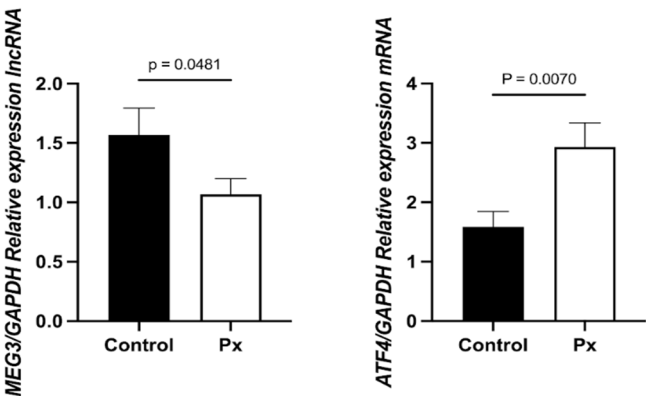


Figure 1. Expression of MEG3 and ATF4 in STEMI patients vs healthy controls. Gene expression of MEG3 and ATF4 was determined by RT-qPCR using RPLP0 as reference for the 2^{-ΔΔCt} method. Differences were tested by the T-student test. Data are presented as means ± SD.

Further subgroup analysis revealed that MEG3 expression was significantly lower in STEMI patients who experienced MACE compared to those who did not (0.8974, 0.4186–1.4131 vs. 1.2259, 0.5516–2.3964; p = 0.0342). Conversely, ATF4 expression was significantly higher in the MACE group (2.8950, 0.7559–4.3287 vs. 2.3498, 1.0821–3.6903; p = 0.0396) (Figure 2).

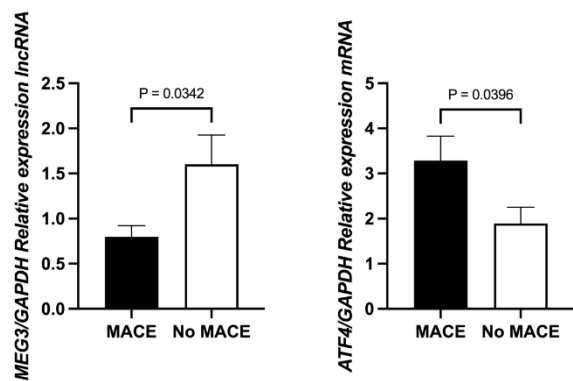


Figure 2. Expression of *MEG3* and *ATF4* in STEMI patients who experienced MACE vs to those who did not. Gene expression of *MEG3* and *ATF4* was determined by RT-qPCR using *RPLP0* as reference for the $2^{-\Delta\Delta Ct}$ method. Differences were tested by the T-student test. Data are presented as means $\pm$ SD.

ROC curve analysis was performed to assess the predictive potential of *MEG3* and *ATF4* for MACE. *MEG3* showed a modest discriminative ability, with an AUC of 0.6490 (0.4760 to 0.8221; $p = 0.0924$). The optimal cut-off value was < 0.3201 based on the Youden index. *ATF4* demonstrated slightly better discriminative performance, with an AUC of 0.7127 (0.5862 to 0.8393; $p = 0.0107$) and an optimal cut-off value of > 0.003391 (Figure 3).

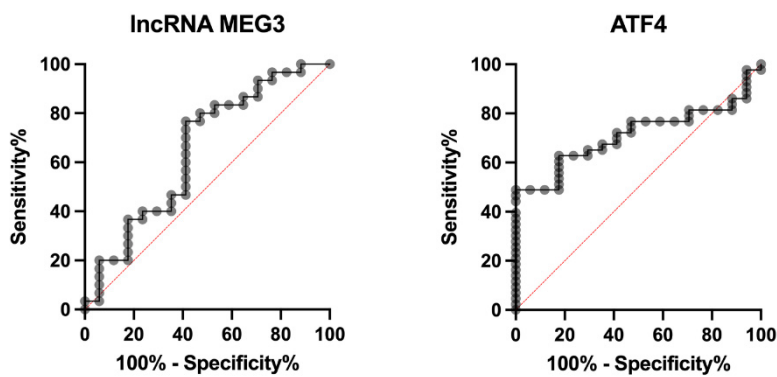


Figure 3. ROC curve analysis to the predictive potential of *MEG3* and *ATF4* for MACE.

Finally, correlation analyses revealed that *MEG3* expression was positively associated with CK-MB levels ($r = 0.3978$, 0.0630 to 0.6520; $p = 0.0219$). *ATF4* expression was positively correlated with cTnT ($r = 0.3328$, 0.0284 to 0.5810; $p = 0.0335$) and inversely correlated with left ventricular ejection fraction (LVEF; $r = -0.4283$, -0.6503 to -0.1390 ; $p = 0.0052$). Moreover, a significant positive correlation was observed between *MEG3* and *ATF4* expression levels ($r = 0.4048$, 0.1425 to 0.6140; $p = 0.0035$) (Table 2).

Table 2. Correlation of variables between *MEG3*, *ATF4*, and IAMEST variables.

	<i>MEG3</i>			<i>ATF4</i>		
	Rho	95% CI	P-value	Rho	95% CI	P-value
CnTn	0.2640	-0.8723–0.5568	0.0696	0.3328	0.02804–0.5810	0.0335
CK-MB	0.3978	0.0630–0.6520	0.0219	-0.0268	-0.3318–0.2831	0.8676
CRP	-0.1836	-0.4956–0.1705	0.3065	0.0223	-0.2873–0.3277	0.8898
Albumin	0.2068	-0.1529–0.5181	0.2562	0.1267	-0.1924–0.4216	0.4360
NT-proBNP	-0.2286	-0.5303–0.1244	0.2006	-0.1356	-0.4255–0.1796	0.3980

TIMI	-0.0954	-0.4249–0.2562	0.5971	-0.1528	-0.4398–0.1625	0.3403
GRACE	0.0297	-0.3168–0.3693	0.8695	-0.2073	-0.4841–0.1072	0.1935
LVEF	0.1051	-0.2472–0.4328	0.5606	-0.4283	-0.6503–0.1389	0.0052

Data are presented as Pearson correlation coefficient (r) with 95% confidence intervals (95% CI). Significance P values are in bold. CnTn: Cardiac muscle troponin T; CK-MB: Creatine kinase-myocardial band; CRP: C-Reactive protein; LVEF: Left ventricular ejection fraction.

3. Discussion

Our results demonstrate a significant reduction in *MEG3* expression in patients with STEMI compared to healthy controls. Moreover, within the MI cohort, *MEG3* expression was markedly lower in patients who experienced MACE than in those without such events.

These findings contrast with a recent study reporting increased *MEG3* expression in patients with acute MI compared to with non-acute presentations [11]. Similarly, Liu et al. found that *MEG3* expression was positively correlated with serum levels of CK-MB and cardiac troponin I [12]. Mechanistically, *MEG3* silencing has been shown to exert cardioprotective effects by attenuating apoptosis and autophagy, primarily through the regulation of GRP78, ATF4, and CHOP expression [13]. In addition, the downregulation of *MEG3* has been reported to alleviate hypoxia-induced cardiomyocyte injury via modulation of miR-325-3p [13]. In light of this evidence, the decreased *MEG3* expression observed in our STEMI patients may represent a compensatory response aimed at limiting myocardial damage via suppression of pro-apoptotic and pro-autophagic signaling pathways [14].

We also observed a significant increase in *ATF4* expression in STEMI patients relative to healthy controls. Notably, *ATF4* levels were elevated in patients who developed MACE, and correlated positively with cTnT and inversely with LVEF, suggesting a potential role in the severity of myocardial injury. Experimental models have consistently shown that ATF4 plays a critical role in I/R injury. For example, suppression of ATF4—via WTAP knockdown [15], melatonin administration [16], or treatment with empagliflozin [17]—has been shown to mitigate myocardial apoptosis, autophagy, and cardiac tissue damage. However, contrasting evidence exists. Cardiomyocyte-specific deletion of *Atf4* in mice has been shown to exacerbate cardiac dysfunction, fibrosis, and apoptosis, suggesting that ATF4 may serve a dual function, both balancing cellular stress responses and maintaining cardiac homeostasis [18].

Interestingly, our study also identified a positive correlation between *MEG3* and *ATF4* expression, despite the overall downregulation of *MEG3* in STEMI patients. This finding is consistent with prior studies indicating that *MEG3* may positively regulate ATF4 by repressing miR-214, a microRNA known to negatively regulate ATF4 [19]. This interaction supports the existence of a complex *MEG3–ATF4* regulatory axis, which may influence the balance between injury and repair processes during myocardial infarction.

A key strength of this study is its focus on human subjects, thereby extending prior findings derived primarily from animal models. In addition, the study reached sufficient statistical power for most comparisons. Nonetheless, some limitations should be acknowledged. The relatively small sample size may reduce the robustness of subgroup analyses and limit generalizability. Moreover, incomplete processing of the entire *MEG3–ATF4* regulatory pathway (AXIS) may have impacted the interpretation of our results.

4. Materials and Methods

4.1. Study Design

A cross-sectional study was conducted between July 2023 to August 2024 at the Instituto Nacional de Cardiología Ignacio Chávez in Mexico City, a tertiary academic center specializing in the study and management of cardiovascular diseases.

Patients were eligible for inclusion if they met the following criteria: (1) first-time diagnosis of STEMI, (2) hemodynamic stability at the time of hospital admission, and (3) infarction localized primarily to the anterior wall. Exclusion criteria comprised the presence of clinical infection, active malignancy, or autoimmune disease. In addition, a group of healthy blood donors was included as reference controls.

4.2. *Diagnosis of ST-Segment Elevation Myocardial Infarction*

STEMI was defined according to international guidelines as an ST-segment elevation of >1 mm in at least two contiguous leads on electrocardiography, in the presence of ischemic symptoms and elevated high-sensitivity cardiac troponin levels [20].

4.3. *Diagnosis of Major Adverse Cardiovascular Events*

Major adverse cardiovascular events (MACE) were defined in our study as a composite outcome including reinfarction, angina, heart failure, stroke, or death.

4.4. *Laboratory Procedures*

Blood samples were collected at Coronary Care Unit admission. Total RNA was extracted from peripheral blood samples using TRIzol LS Reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. Briefly, 400 μ L of whole blood was mixed with 700 μ L of TRIzol reagent. After adding 140 μ L of chloroform, the mixture was shaken vigorously for 15 seconds, incubated at room temperature for 5 minutes, and centrifuged at $12,000 \times g$ at 4°C for 15 minutes. The aqueous phase was transferred to a new tube, and an equal volume of isopropanol was added. After a 30-minute incubation, the mixture was centrifuged again under the same conditions. The resulting RNA pellet was washed twice with 1,000 μ L of 75% ethanol and centrifuged at $12,000 \times g$ at 4°C for 10 minutes. The pellet was then air-dried and resuspended in DEPC-treated water. RNA quality was assessed using a NanoDrop spectrophotometer, NanoDrop 2000 Thermo-Scientific (USA), and purity was confirmed by a 260/280 absorbance ratio between 1.8 and 2.0.

cDNA synthesis was performed using the QuantiTect Reverse Transcription Kit (Cat. No. 205313, QIAGEN, Hilden, Germany), and qPCR was carried out using the QuantiNova SYBR Green PCR Kit (Cat. No. 216915, QIAGEN, Hilden, Germany), following the manufacturer's protocols using CFX Opus 96 Touch Real-Time PCR Detection System (Bio-Rad, California, USA). Primer sequences were pre-designed by QIAGEN for the following targets: MEG3 (RT² lncRNA qPCR Assay, Cat. No. SBH0448235) and ATF4 (Cat. No. QT00074466). Gene expression levels were quantified using the $2^{-\Delta\Delta\text{CT}}$ method, with Glyceraldehyde-3-Phosphate Dehydrogenase (GAPDH) as the reference gene.

4.5. *Ethical Approval*

All participants provided written informed consent authorizing the use of their clinical data and biological samples for research purposes. The study protocol was approved by the Bioethics Committee of the Instituto Nacional de Cardiología Ignacio Chávez (Protocol No. 23-1377). All procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (2013) and its subsequent amendments.

4.6. *Statistical Analyses*

Categorical variables were described as frequencies and percentages, while continuous variables were expressed as medians with interquartile ranges (IQR). Differences between medians were evaluated using the unpaired t-test with Welch's correction. Correlations were assessed using the Pearson correlation coefficient (r) with 95% confidence intervals (95% CI).

The predictive value of MEG3 and ATF4 expression levels for STEMI was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was reported with 95% CI, and the optimal cut-off point was determined using the Youden index.

All analyses were two-tailed, and a p-value <0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism version 10 (GraphPad Software, La Jolla, CA, USA).

5. Conclusions

In conclusion, our results suggest that dysregulation of the lncRNA *MEG3* and the transcription factor *ATF4* is a characteristic feature of STEMI and is associated with adverse clinical outcomes. Specifically, *MEG3* expression is reduced while *ATF4* is increased in STEMI patients, and both molecules show significant correlations with biomarkers of myocardial injury and functional impairment.

Author Contributions: conceptualization, A.H.-D.; methodology, FJR-U, Y.J.-V, LMA-G, AH-D.; software, AH-D, LMA-G, FJR-U; validation, FJR-U, DS-L, Y.J.-V, MB-P, AA-M, HG-P, M-C, LMA-G., and AH,D.; formal analysis, AH-D, LMA-G, FJR-U.; investigation, FJR-U, AH-D.; resources, AH-D.; data curation, FJR-U, AH-D ; writing—original draft preparation, FJR-U; writing—review and editing, FJR-U, AH-D, LMA-G .visualization, AH-D.; supervision, LMA-G, AH-D.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the Instituto Nacional de Cardiología Ignacio Chávez (protocol code: 23-1377 and date of approval: May 25, 2023).” for studies involving humans.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Acknowledgments: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

ATF4	Activating transcription factor 4
BMI	Body mass index
CAD	Coronary artery disease
ceRNA	Competitive endogenous RNA
CHOP	C/EBP homologous protein
CK-MB	Creatine kinase–MB
cTnT	Cardiac troponin T
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DEPC	Diethyl pyrocarbonate
ER	Endoplasmic reticulum
GAPDH	Glyceraldehyde-3-phosphate dehydrogenase
GRACE	Global Registry of Acute Coronary Events
GRP78	Glucose-regulated protein 78
hsCRP	High-sensitivity C-reactive protein
I/R	Ischemia/reperfusion
lncRNA	Long non-coding RNA
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular events
MEG3	Maternally expressed gene 3
MI	Myocardial infarction
miR-214	MicroRNA-214
NT-proBNP	N-terminal pro-B-type natriuretic peptide

RPLP0	Ribosomal protein lateral stalk subunit P0
SBP	Systolic blood pressure
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction
WTAP	Wilms tumor 1–associating protein

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