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Alteration of RNA methylation and hypertrophic maladaptation via TORC1-S6K1

M. Moscati[1]

1 Italy

1. ABSTRACT

The analyzed study evaluated how the loss of FTO, an enzyme that removes a specific RNA modification called m6A, affects the heart's adaptation to pressure overload. In mice with FTO loss in cardiomyocytes and in human heart cells derived from induced pluripotent stem cells, the initially compensatory growth response was reduced. In its place, cardiac dilation, fibrosis, cell death, and signs of impaired clearance of damaged cellular components appeared.The research contributes to the section of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi dedicated to the potential damage caused by persistent hyperactivation of the mTORC1-S6K1 axis. The study links the loss of FTO to an increase in the activity of this pathway, a reduction in autophagy, and signs of apoptosis. Independent evidence supports the biological coherence of this chain, including animal data and an observational association in humans. However, the specific FTO-PRAS40-TFEB mechanisms and the therapeutic efficacy of inhibiting this pathway require clinical confirmation.

ONLINE ARTICLE

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MISSION

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Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

Free from political, industrial and commercial influence, the journal stands as an authoritative and independent editorial space, dedicated to promoting scientific culture, professional development and the growth of health awareness among the public.

2. ANALYZED STUDY

The research question was whether the reduction of FTO in cardiomyocytes would compromise the heart's initial adaptation phase to an increased workload. FTO is an RNA demethylase, an enzyme capable of removing the m6A chemical signal from messenger RNA. This modification can influence how much an RNA is translated into protein, without necessarily changing the amount of the RNA itself.The authors' hypothesis was that FTO deficiency would alter RNA regulation and shift the heart from an initially compensatory growth toward unfavorable remodeling. The point relevant to paragraph 4.7 of the book concerns, above all, the segment: loss of FTO hyperactivation of mTORC1-S6K1 reduced autophagy and increased cardiomyocyte death.The study can demonstrate that, in the models used, the loss of FTO is accompanied by these alterations and that pharmacological inhibition of mTORC1-S6K1 attenuates some cellular outcomes. However, it cannot demonstrate that the same mechanism causes heart failure in people, nor that inhibitors of this pathway are effective or safe treatments for this condition.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The authors used eight-week-old adult mice with selective deletion of FTO in cardiomyocytes, compared with control mice carrying the same Cre component but without the deletion of the Fto gene. The animals underwent transverse aortic constriction, a surgical procedure that increases the resistance against which the heart must pump and replicates pressure overload. Sham animals underwent a similar procedure without aortic constriction.One week after surgery, echocardiography, left ventricular weight analysis, histology for cell size and fibrosis, TUNEL staining to identify cells with DNA fragmentation consistent with apoptosis, and protein analysis were performed. Sample sizes varied according to the experiment: for echocardiographic parameters, 3 to 11 animals per group were reported; for some histological analyses, 3 or 4 animals per group were reported.To study RNA regulation, the authors performed MeRIP-seq, a technique that enriches and sequences m6A-containing RNAs, in the left ventricles of the mice. They also used cardiomyocytes derived from human induced pluripotent stem cells, in which FTO was reduced using small interfering RNAs. In these cells, they measured markers of mTORC1-S6K1, autophagy, and apoptosis, and used rapamycin and PF-4708671 to inhibit mTORC1 and S6K1, respectively. The number of human cell donors and detailed inclusion criteria are not reported in the available material.

4. RESULTS

In practical terms, mice lacking FTO in cardiomyocytes did not develop an adequate initial structural response to pressure overload. One week after aortic constriction, the ejection fraction—the percentage of blood pumped out of the ventricle with each contraction—was 25% in FTOcKO mice compared to 45% in controls subjected to the same procedure; the difference was statistically significant with P<0.0001. The internal diameter of the left ventricle was larger in FTOcKO mice, 4.8 mm compared to 3.9 mm in controls, also with P<0.0001.This functional deterioration was accompanied by increased dilation and fibrosis. Unlike the controls, FTOcKO mice did not show an adequate increase in relative wall thickness or an increase in the cross-sectional area of cardiomyocytes following the overload. The authors therefore interpreted the clinical picture as maladaptive dilatative remodeling, rather than compensatory hypertrophy.In human cardiac cells, FTO silencing reduced basal cell size and attenuated the size increase induced by endothelin-1, a signal that promotes hypertrophy. RNA analyses revealed increased m6A methylation of AKT1S1 and TFEB transcripts. AKT1S1 encodes PRAS40, a protein that normally helps to inhibit mTORC1; TFEB is a regulator of lysosome formation and autophagy.Consistent with this hypothesis, PRAS40 and TFEB proteins decreased in cells with reduced FTO, while mTORC1-S6K1 activation signals increased: phosphorylation of S6K1, ribosomal protein S6, and, in human cells, also 4E-BP1. Phosphorylation is a chemical signal that can modify a protein's activity; in this context, it indicates increased activity of the mTORC1 pathway.The loss of FTO also increased markers of apoptosis, including cleaved caspase-3 and PARP, and the number of TUNEL-positive cells. Regarding autophagy, the authors observed an increase in p62 and a reduction in

LC3-II under basal conditions, as well as reduced autophagosome formation in the tandem RFP-GFP-LC3 assay. Taken together, these data are compatible with impaired autophagic flux, meaning a reduced ability of the cell to properly form and dispose of structures destined for intracellular recycling.Finally, in human cardiomyocytes with silenced FTO, rapamycin and PF-4708671 reduced mTORC1-S6K1 pathway signals and attenuated apoptosis. The S6K1 inhibitor also recovered some growth markers and the response to endothelin-1. These results support a functional role for the pathway in the cellular model, but they do not establish that the drug can correct cardiac remodeling in the human body.

5. INTERPRETATION

The key finding is that mTORC1-S6K1 does not simply act as a growth switch. Under physiological conditions, controlled activation of this pathway helps the cardiac cell produce proteins and adapt to increased workload. In the study analyzed, however, the loss of FTO was associated with persistent excessive activation of the mTORC1-S6K1 branch, accompanied by reduced autophagy, cellular atrophy, and apoptosis.The detail proposed by the authors is as follows: the increase in m6A on the AKT1S1 transcript would reduce the amount of the PRAS40 protein, thereby diminishing a brake on mTORC1; in parallel, the alteration of the TFEB transcript would reduce a protein important for autophagy. The consequence would be an excess of anabolic signaling combined with a reduced capacity to recycle damaged cellular components.The segment actually documented by the publication is therefore the experimental relationship between FTO loss, increased mTORC1-S6K1 markers, autophagy alterations, and cardiomyocyte damage. The complete sequence FTO AKT1S1/PRAS40 mTORC1-S6K1 and FTO TFEB autophagy is biologically plausible and supported by multiple measurements, but part of the causal relationship remains inferential: the authors did not selectively restore PRAS40 or TFEB to verify if this was sufficient to correct all the observed effects.

6. INDEPENDENT CONFIRMING EVIDENCE

Independent confirmation of the cardioprotective role of FTO comes from a study that integrated human samples, pig and mouse models, and primary cardiomyocytes. In failing hearts and cardiomyocytes exposed to hypoxia, FTO was reduced and m6A methylation was increased. In animals with myocardial infarction, increasing FTO in the heart attenuated the reduction in contractile function and fibrosis. This study does not directly examine S6K1, but it confirms the upstream part of the narrative: the reduction of FTO and the alteration of RNA methylation can contribute to worse cardiac function [1].A second study, conducted in mice treated with isoproterenol and in neonatal rat cardiomyocytes, examined the link between mTORC1 and cellular damage more directly. Increased mTORC1 was associated with a reduction in TFEB-regulated genes, impaired autophagic flux, and necroptosis, a regulated form of cell death. Pretreatment with rapamycin attenuated cardiomyocyte necrosis, inflammation, and alterations in autophagic flux. This mechanistically confirms the part of the chain suggesting that mTORC1 hyperactivation can reduce autophagy and promote cardiac damage, albeit in a model of excessive catecholaminergic stimulation rather than FTO loss [2].Relevance in humans is suggested by an observational study of 52 people with non-ischemic dilated cardiomyopathy and 10 controls with normal ventricular function. The myocardial area positive for phosphorylated S6 protein, used as an indicator of mTORC1 activity, was approximately ten times greater in patients than in controls: 2.0±2.2% versus 0.2±0.2%, $P<0.01$. A higher signal was associated with greater myocardial fibrosis, with a correlation of $r=0.46$ and $P<0.01$. Five-year event-free survival was numerically lower in the group with high activity, 52.9% versus 81.6%, but the difference was not statistically significant, $P=0.10$. The work does not demonstrate causality, but it makes the hypothesis that persistently high mTORC1 activation is linked to unfavorable remodeling biologically and clinically consistent [3].These findings do not identically reproduce the molecular sequence of the original study. However, they build a convergent chain: reduced FTO and increased m6A can worsen cardiac function; hyperactive mTORC1 can hinder autophagy and promote cell death; in humans, elevated markers of

the mTORC1-S6K1 axis are associated with fibrosis in dilated cardiomyopathy.

7. CONFLICTING EVIDENCE

An important element of context is that mTORC1 is not harmful under all conditions. In adult mice with cardiac deletion of Raptor, an essential component of mTORC1, the loss of the pathway resulted in dilated cardiomyopathy and high mortality within six weeks. After pressure overload, the animals did not develop an adaptive hypertrophy phase and, after just one week, already exhibited severe dilation, lower phosphorylation of S6K1 and 4E-BP1, increased apoptosis, and increased autophagy [4].This result does not directly contradict the analyzed study, because it concerns a strong reduction of mTORC1 rather than its hyperactivation. However, it limits a simplistic interpretation: both too low and excessive or persistent activity of the pathway can be unfavorable. The direction of the effect depends on the intensity, duration of the stimulus, phase of remodeling, and metabolic context. No directly conflicting evidence sufficiently relevant to the specific FTO-PRAS40-TFEB axis has been identified; this does not prove the absence of contrary results.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent research used to verify the individual steps of the narrative.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Animal and cellular	FTOcKO mice subjected to pressure overload; human iPSC-derived cardiomyocytes	Loss of FTO increases mTORC1-S6K1 signaling, impairs autophagy, and increases apoptosis; pathway inhibition attenuates certain cellular outcomes	direct confirmation	moderate
[1]	Animal, cellular, and human samples	Human hearts with heart failure, pig and mouse models, primary cardiomyocytes	Reduced FTO and increased m6A are associated with lower contractile function; increasing FTO attenuates dysfunction and fibrosis in mice	indirect confirmation	moderate
[2]	Animal and cellular	Mice treated with isoproterenol and neonatal rat cardiomyocytes	Hyperactivation of mTORC1 associated with reduced autophagy and necroptosis; rapamycin attenuates damage	direct confirmation	moderate

[3]	Observational	52 patients with non-ischemic dilated cardiomyopathy and 10 controls	Higher myocardial mTORC1 activity associated with greater fibrosis; numerically worse but non-significant prognosis	biologically consistent evidence	low
[4]	Animal	Adult mice with cardiac Raptor ablation subjected to pressure overload	Marked reduction of mTORC1 prevents adaptive hypertrophy and accelerates dilation and heart failure	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed convincingly supports, within its experimental models, that the loss of FTO can shift the cardiomyocyte from a growth adaptation toward a state of atrophy, apoptosis, and impaired autophagy. The most relevant point for the book is the hyperactivation of mTORC1-S6K1 as a possible component of the damage, rather than a simple indicator of cell growth.Independent evidence is consistent with this interpretation and indicates that persistent activation of mTORC1 can promote autophagy defects and cardiac cell death. However, the picture is context-dependent: severe inhibition of the same pathway can, in turn, compromise the heart's adaptive response. The narrative is therefore well-supported at a mechanistic level, but requires validation in humans before any therapeutic application.

Aggiornato al 24/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

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