LIFE Science Hub
JOURNAL OF SCIENCE
EXPANDING KNOWLEDGE ABOUT NUTRITION AND HEALTH

ORIGINAL RESEARCH
ISSN 2845-7501

Synthesis of essential fatty acids and its regulation in mammals - Review of the evidence

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1. ABSTRACT

The analyzed publication examines how mammals regulate the production of long-chain polyunsaturated fatty acids. The central point is Δ6-desaturase, an enzyme encoded by the FADS2 gene, which initiates the transformation of essential fatty acids introduced through the diet. The authors report that SREBP-1c, a transcription factor that regulates gene activity, activates the transcription of Δ6-desaturase and that highly unsaturated fatty acids exert feedback control, reducing this signal.In paragraph 5.3.1 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the study contributes to the passage stating that the activation of SREBP-1c increases the cellular capacity to initiate the desaturation of omega-3 fatty acids. Independent studies in rat hepatocytes, rodent livers, goat mammary cells, and human tumor cells confirm that SREBP can increase FADS2 expression or bind to regulatory regions of the gene. However, this evidence does not prove that hyperinsulinemia directly causes inflammation in humans through this pathway.

ONLINE ARTICLE

ARTICLE INFORMATION

Published: November 25, 2026
Updated: November 25, 2026

DOI 10.5281/zenodo.24529579

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2. ANALYZED STUDY

The research question was how the amount of highly unsaturated fatty acids in mammalian tissues is maintained within narrow limits. The hypothesis discussed by the authors is that Δ6-desaturase, the enzyme that inserts a double bond into certain essential fatty acids, represents a decisive control point and is regulated by SREBP-1c.The relevance to the paragraph under consideration is specific: the publication subject to the Evidence Review describes SREBP-1c as a transcriptional regulator of the Δ6-desaturase gene. This corresponds to the initial segment of the narrative: increased SREBP-1c activity increased capacity to initiate the desaturation of omega-6 essential fatty acids.The analyzed study can therefore support a gene regulation mechanism. However, it cannot, on its own, demonstrate that the persistent activation of this mechanism causes an increase in inflammation, eicosanoid production, or disease risk in humans.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The available material consists only of the abstract. The publication is presented as a narrative synthesis of evidence regarding the biosynthesis of essential fatty acids and its regulation in mammals, including experimental results previously obtained by the authors.The abstract mentions transfection experiments in HepG2 cells, a cell line derived from human liver cancer. In these experiments, constructs containing regulatory regions of the human Δ6-desaturase gene and a nuclear form of SREBP-1c were introduced. Analyses of promoter mutation—that is, the DNA region that controls the activation of a gene—are also referenced.The number of experiments, sample selection criteria, number of biological replicates, concentrations used, statistical tests, significance values, and detailed quantitative results are not reported in the available material. There are no human participants or clinical follow-ups described in the abstract.

4. RESULTS

The central finding is that SREBP-1c activates the transcription of the human Δ6-desaturase gene. In simple terms, when this gene regulator is active, the cell receives a stronger signal to produce the enzyme that initiates the transformation of essential fatty acids into more unsaturated products.The authors report that a 90-base pair region of the Δ6-desaturase promoter was necessary for both activation by SREBP-1c and suppression induced by highly unsaturated fatty acids. Mutation analyses identified a sterol response element, termed SRE-2, as essential for both effects. The abstract does not report the numerical magnitude of the increase in gene expression nor P-values.The publication also reports that highly unsaturated fatty acids reduce the activity of the Δ6-desaturase gene through the same regulatory element. This is a feedback control: when certain end products are available in high quantities, the drive to produce more from precursors is reduced.Finally, the authors describe a role for peroxisomal beta-oxidation, that is, the degradation of fatty acids in cellular peroxisomes, in the synthesis of docosahexaenoic acid. This result belongs to the general discussion of the study, but it is not the passage for which the publication was used in the book's paragraph.

5. INTERPRETATION

The most immediate biological significance is that SREBP-1c does not only regulate the production of new saturated and monounsaturated fats. It can also increase the expression of FADS2, the Δ6-desaturase gene, and therefore the availability of the enzyme that opens the metabolic pathway for polyunsaturated fatty acids.In the omega-6 pathway, linoleic acid is first converted into gamma-linolenic acid by Δ6-desaturase; this is followed by chain elongation and the action of Δ5-desaturase, which contribute to the formation of DGLA and, subsequently, arachidonic acid. For this reason, increasing Δ6-desaturase may increase the cell's potential capacity to process linoleic acid. However, this does not equate to demonstrating that arachidonic acid necessarily increases in every tissue or under every dietary condition.In section 5.3.1 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, the segment directly documented by the original study is SREBP-1c transcription of Δ6-desaturase. The subsequent link between this regulation and greater availability of arachidonic acid requires other enzymes, the availability of substrates,

and the tissue context. The final step toward inflammatory mediators therefore remains a biologically plausible extension, but not a clinical consequence directly demonstrated by the analyzed publication.

6. INDEPENDENT SUPPORTING EVIDENCE

Particularly relevant independent confirmation comes from experiments in rodent liver and primary hepatocytes. Wang and colleagues observed that an increase in the nuclear form of SREBP-1c increased the expression of Δ6-desaturase in the models studied. In primary rat hepatocytes, overexpression of SREBP-1c increased the Δ6-desaturase transcript by approximately 4.8-fold. The result supports the direction of the relationship proposed in the paragraph: higher SREBP-1c activity is associated with greater expression of the enzyme. However, the same study shows that PPARα, another transcriptional regulator, can also modify desaturase expression; therefore, regulation does not depend on a single factor [1].A second study verified the direct relationship between SREBP1 and FADS2 in goat mammary gland epithelial cells. The authors combined experiments using promoters, targeted mutations, chromatin immunoprecipitation—a technique that verifies whether a protein binds to a specific region of DNA—and CRISPR interference. SREBP1 bound to two regulatory elements of the FADS2 promoter; blocking them reduced FADS2 expression. Furthermore, FADS2 overexpression increased cellular concentrations of DGLA. This evidence directly confirms the transcriptional mechanism, but it concerns a species and tissue different from the human liver [2].Further validation was obtained in human and murine tumor cells. Triki and colleagues showed, through chromatin immunoprecipitation, that SREBP-1 can bind to the FADS2 promoter; an increase in SREBP increased FADS2 expression. In this model, however, the focus was primarily on the production of sapienic acid in tumor cells. The work confirms the regulation of FADS2 by SREBP, but it does not specifically demonstrate the conversion of linoleic acid into DGLA or arachidonic acid in a healthy organism [3].Taken together, these studies reconstruct a convergent chain: SREBP-1c can be activated by nutritional and insulin signals; once present in the nucleus, it can bind to regulatory elements of the FADS2 gene and increase its transcription; a greater quantity of Δ6-desaturase increases the ability to initiate the transformation of polyunsaturated precursors. The most direct evidence is experimental and based on cells or animals; a clinical demonstration that quantifies the complete pathway leading to inflammatory eicosanoids in humans is still lacking.

7. CONFLICTING EVIDENCE

No directly conflicting evidence of sufficient relevance has been identified; this does not prove the absence of contrary results.However, there are important contextual elements. In the study on liver models, the expression of Δ6-desaturase was also regulated by PPARα, a transcription factor linked to fatty acid metabolism. This finding does not contradict the action of SREBP-1c, but it indicates that the FADS2 gene responds to multiple metabolic signals and that the effect of SREBP-1c can vary based on nutritional status, tissue, and species [1].Furthermore, the available direct confirmations are derived from rodent hepatocytes, goat mammary cells, or tumor cells. These systems are useful for establishing a mechanism, but they do not allow for the automatic transfer of results to human monocytes, people with hyperinsulinemia, or inflammatory clinical outcomes.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication under review from the independent evidence selected to confirm the specific passage of the paragraph.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative synthesis with promoter experiments mentioned in the abstract	HepG2 cells and human Δ6-desaturase gene; full details not available	SREBP-1c activates Δ6-desaturase transcription via an SRE element in the promoter	biologically consistent evidence	moderate
[1]	Animal and cellular	Rodent liver and primary rat hepatocytes	SREBP-1c overexpression increases Δ6-desaturase transcript expression	direct confirmation	moderate
[2]	Cellular	Goat mammary epithelial cells	SREBP1 binds to the FADS2 promoter; blocking regulatory sites reduces FADS2 expression	direct confirmation	moderate
[3]	Cellular	Human and murine tumor cell lines	SREBP-1 binds to the FADS2 promoter and increases its expression	indirect confirmation	preliminary

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication provides relevant support for the claim that SREBP-1c can increase the transcription of Δ6-desaturase. Independent evidence confirms that SREBP can regulate FADS2 through binding to specific DNA regions and can increase its expression in various experimental models.The narrative is therefore well-supported at a mechanistic level. However, the link to downstream metabolic consequences, such as the increase in arachidonic acid, remains moderately supported, and the further step toward a clinically relevant amplification of pro-inflammatory pathways requires validation in humans.

Aggiornato al 25/11/2026. 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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