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Fish Oil-Derived Omega-3 Fatty Acids Modulate Histone Acetylation in Adipocyte Differentiation

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ABSTRACT

Background: Adipocyte differentiation is governed by the transcription factors PPARgamma and C/EBP, whose activity at target gene loci is permitted or restrained by histone acetylation, a reversible chromatin mark written by histone acetyltransferases and erased by histone deacetylases. Dietary fish oil-derived omega-3 polyunsaturated fatty acids, principally eicosapentaenoic acid and docosahexaenoic acid, are established modulators of adipocyte biology, but their specific relationship to histone acetylation at adipogenic loci has not been systematically synthesized. Objective: This narrative review integrates published biochemical, cell-culture, and rodent literature to examine how omega-3 fatty acids intersect with the histone acetylation machinery during adipocyte differentiation. Methods: We reviewed studies of docosahexaenoic acid and eicosapentaenoic acid effects on PPARgamma/C/EBP signaling in 3T3-L1 and primary adipocytes, the enzymology of histone acetyltransferases and deacetylases (HDAC1/2, HDAC3, SIRT1, p300/CBP) in adipogenesis, and direct evidence of omega-3-induced histone acetylation change at adipose gene loci in vivo. Findings: Omega-3 fatty acids modulate adipogenesis through direct PPARgamma ligand binding, stage-dependent and dose-dependent effects on lipid accumulation, and regulation of PPARgamma Ser273 phosphorylation, while independently characterized deacetylases (HDAC1/2, HDAC3, SIRT1) govern the same transcriptional program. Direct evidence that dietary fish oil increases histone H3 acetylation and reduces HDAC1, HDAC2, and HDAC6 occupancy has been demonstrated at the leptin promoter in diet-induced obese mice, accompanied by lower plasma and adipose leptin. Conclusions: Available evidence supports a biochemically coherent, but still largely preclinical, model in which omega-3 fatty acids engage adipocyte differentiation partly through histone acetylation-dependent mechanisms; human studies pairing controlled fish oil supplementation with locus-resolved chromatin profiling of adipose tissue are needed to establish translational relevance.

Keywords: *omega-3 fatty acids; histone acetylation; adipocyte differentiation; histone deacetylase; PPAR-gamma*

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Introduction

Adipocyte differentiation is governed by a tightly ordered transcriptional cascade in which peroxisome proliferator-activated receptor gamma (PPARγ) and the CCAAT/enhancer-binding proteins (C/EBPα, C/EBPβ, C/EBPδ) act as master regulators, driving preadipocytes through mitotic clonal expansion into lipid-laden, insulin-responsive mature adipocytes [1]. This transcriptional program does not unfold on naked DNA; it is permitted or restrained by the chromatin state at PPARγ and C/EBP target loci, and histone acetylation is among the most consequential of these chromatin marks. Acetylation of lysine residues on histone H3 and H4 tails, deposited by histone acetyltransferases (HATs) such as p300/CBP and removed by histone deacetylases (HDACs), neutralizes the positive charge of the histone tail, loosens nucleosome-DNA contacts, and creates docking sites for bromodomain-containing coactivators, thereby converting condensed, transcriptionally silent chromatin into an open, permissive state at adipogenic enhancers and promoters [2,3]. The balance between HAT and HDAC activity at the Pparg and Cebpa loci, and at their downstream target genes, is now recognized as a rate-limiting determinant of whether a preadipocyte commits to, or resists, terminal differentiation [4].

In parallel with this chromatin-focused view of adipogenesis, a substantial nutritional biochemistry literature has established that dietary long-chain omega-3 polyunsaturated fatty acids (n-3 PUFA) derived from fish oil, principally eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), exert potent and often opposing effects on adipocyte biology relative to

saturated and omega-6 fatty acids. DHA and EPA can act as direct ligands for PPARγ and other nuclear receptors [5], signal through the cell-surface long-chain fatty-acid receptor GPR120/FFAR4 [6,7], and modulate adipogenic and lipogenic gene programs in a manner that depends on fatty acid identity, concentration, and the maturational stage of the target cell [8,9]. What has been less thoroughly synthesized is the specific intersection of these two literatures: the evidence that n-3 PUFA act, at least in part, by remodeling histone acetylation at adipogenic and adipokine gene loci, rather than solely through classical ligand-activated transcription factor signaling.

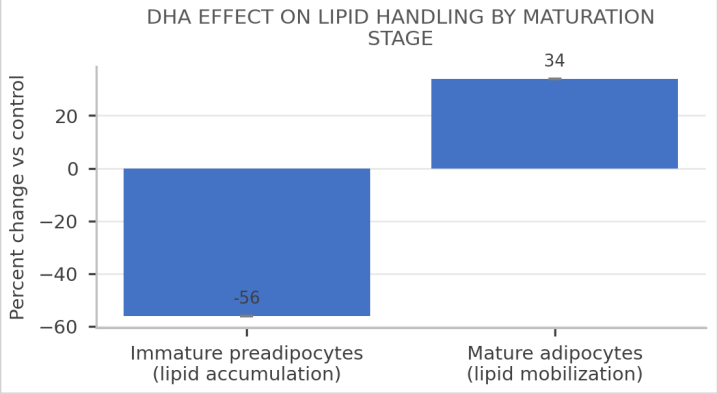
This narrative review synthesizes published cell-culture, rodent, and biochemical studies that bear on this intersection. We first summarize how omega-3 fatty acids modulate the core adipogenic transcription factors PPARγ and C/EBP, then turn to the enzymatic machinery of histone acetylation and deacetylation that operates during adipocyte differentiation, then examine the direct and indirect biochemical routes by which fatty acids, including n-3 PUFA, engage histone-modifying enzymes, and finally consider the translational evidence, from rodent adipose tissue to a limited human literature, that dietary fish oil intake produces measurable changes in histone acetylation at specific adipose gene loci. Throughout, we distinguish mechanistic plausibility, which is well supported, from direct causal demonstration in adipose tissue, which remains comparatively sparse, particularly in humans.

Omega-3 Fatty Acids as Modulators of Adipogenic Transcription Factors

The founding observation in this field is that DHA, added to 3T3-L1 preadipocytes across a concentration range of 25-200 micromolar, inhibits differentiation-associated mitotic clonal expansion, decreases mean lipid droplet size and percent lipid area in a dose-dependent manner, reduces glycerol-3-phosphate dehydrogenase activity, and at concentrations of 100 and 200 micromolar induces preadipocyte apoptosis, while simultaneously increasing basal lipolysis [10]. This early study established that DHA is not simply an inert lipid substrate for triglyceride storage but an active suppressor of the adipogenic program at concentrations achievable in fish-oil-supplemented tissue. Subsequent work has refined this picture by showing that the direction and magnitude of DHA's effect on PPARγ target gene expression depends critically on when, during differentiation, the cell is exposed to the fatty acid: Grigorova and colleagues reported that DHA applied to immature 3T3-L1 preadipocytes markedly inhibited adipogenesis, reducing lipid accumulation by approximately 56%, whereas the same dose applied to mature, fully differentiated adipocytes instead promoted lipid mobilization, increasing it by approximately 34%, indicating that DHA reverses its functional relationship with the PPARγ program as a function of cellular maturation stage rather than acting as a uniform PPARγ agonist or antagonist [8].

A complementary line of evidence addresses how EPA and DHA differentially engage PPARγ post-translational regulation and downstream adipokine output. Song and colleagues found that DHA increased cellular and secreted adiponectin expression in 3T3-L1 adipocytes more effectively than EPA at relatively low concentrations of 50 and 100 micromolar, and that the two fatty acids exerted opposite effects on PPARγ phosphorylation at serine 273, a modification associated with dysregulated adipokine expression in obesity: DHA significantly decreased Ser273 phosphorylation while EPA increased it, demonstrating that structurally similar n-3 PUFA can diverge sharply in their regulation of a single, clinically relevant PPARγ post-translational mark [9]. This fatty-acid-specific divergence is consistent with earlier work in primary human adipocytes showing that EPA, but not the n-6 fatty acid arachidonic acid, promotes acquisition of a brite (brown-in-white) phenotype together with increased mitochondrial respiratory capacity, again underscoring that the n-3 double-bond configuration, not polyunsaturation per se, drives much of the adipogenic and thermogenic gene response [11]. Mechanistically, this fatty-acid-class specificity is consistent with early biochemical work demonstrating that EPA, DHA, and other long-chain polyunsaturated fatty acids and eicosanoids bind directly to the ligand-binding domains of PPARα and PPARγ and activate PPAR-responsive reporter constructs, establishing PUFA as bona fide, if comparatively weak, endogenous PPAR ligands rather than purely membrane-signaling lipids [5]. Together, these transcription-factor-level studies establish that omega-3 fatty acids modulate the PPARγ/C/EBP adipogenic axis through at least three distinct mechanisms operating in parallel: direct nuclear receptor ligand binding, regulation of PPARγ phosphorylation status, and stage-dependent reversal of net effect on lipid accumulation, providing multiple entry points through which the chromatin-level acetylation events discussed in the following section could plausibly be engaged.

DHA exposure reverses its effect on adipocyte lipid handling depending on the maturation stage of the target cell: in immature 3T3-L1 preadipocytes DHA suppresses lipid accumulation, whereas the same dose applied to mature, fully differentiated adipocytes instead promotes lipid mobilization. Values are percent change relative to vehicle-treated control at the corresponding maturation stage, as reported by Grigorova et al. (2025).



Histone Acetyltransferase and Deacetylase Machinery in Adipocyte Differentiation

Independent of any nutritional input, the enzymatic control of histone acetylation is itself a well-characterized determinant of adipogenic competence. Haberland and colleagues demonstrated that combined, but not individual, genetic depletion of HDAC1 and HDAC2 in 3T3-L1 preadipocytes markedly impairs adipocyte differentiation, establishing that these two class I deacetylases act redundantly to license, rather than to simply repress, the terminal differentiation program, a counterintuitive finding given the conventional view of HDACs as transcriptional repressors [12]. This redundant permissive role illustrates that the relationship between global histone deacetylase activity and adipogenic output is not monotonic: some HDAC activity is required for proper progression through differentiation, while excess or mistimed deacetylation at specific loci can be inhibitory. Complementing this class I HDAC data, Ferrari and colleagues showed that adipose-selective ablation of HDAC3 increases histone acetylation at enhancers within the Pparg and Ucp1 loci in white adipose

tissue, activates a futile cycle of simultaneous fatty acid synthesis and oxidation, upregulates browning marker genes including Ucp1, Dio2, Ppara, and Prdm16, and improves cold-induced thermogenic capacity, a phenotype that is abolished by high-fat feeding, together identifying HDAC3 as a locus-specific brake on the acetylation-dependent activation of thermogenic and lipid-handling genes in adipose tissue [13].

Enzymatic regulators of histone acetylation implicated in adipocyte differentiation and their reported functional role.

Enzyme/complex	Class	Locus/pathway affected	Reported functional role in adipogenesis
HDAC1/HDAC2 (combined)	Class I HDAC	PPARγ/C/EBP program (3T3-L1)	Redundantly required to permit differentiation; combined knockdown impairs adipogenesis
HDAC3	Class I HDAC	Pparg and Ucp1 enhancers (white adipose tissue)	Molecular brake on browning; adipose-selective loss increases enhancer acetylation and induces Ucp1, Dio2, Ppara, Prdm16
SIRT1	Class III HDAC (NAD+-dependent)	PPARγ (with NCoR/SMRT)	Represses PPARγ activity, promoting lipolysis and fat mobilization in white adipocytes
p300/CBP	Histone acetyltransferase	C/EBPβ and PPARγ coactivation	Coactivates early adipogenic transcription factors; allosterically activated by short-chain acyl-CoA species

Reviews synthesizing this broader enzymatic landscape have organized the relevant HATs and HDACs by their stage-specific roles across the adipogenic cascade, noting that p300/CBP-family acetyltransferases coactivate C/EBPβ and PPARγ at the initiation of differentiation, whereas specific class I and class III HDACs, including SIRT1, act at later stages to fine-tune PPARγ output and lipid mobilization rather than to simply block differentiation outright [3,4]. The sirtuin family provides a particularly well-characterized example of deacetylase action that intersects directly with fatty acid metabolism: Picard and colleagues showed that SIRT1, a nicotinamide adenine dinucleotide-dependent class III deacetylase, docks onto PPARγ together with the corepressors NCoR and SMRT and represses PPARγ activity, thereby promoting lipolysis and fat mobilization in white adipocytes, a mechanism through which nutrient and energy status, both of which influence NAD+ availability, can be transduced into altered histone and non-histone acetylation at PPARγ target genes [14]. Taken together, this body of work establishes that adipocyte differentiation depends on the coordinated, temporally sequenced action of HATs and HDACs at PPARγ and C/EBP loci, that HDAC activity can be either pro- or anti-adipogenic depending on the specific enzyme, locus, and differentiation stage examined, and that this same acetylation-writing and -erasing machinery is a documented substrate for regulation by fatty acid and NAD+-dependent metabolic signals, setting the stage for omega-3 fatty acids to act as one such nutrient-derived input.

Fatty Acids as Direct and Indirect Regulators of Histone Acetylation

Beyond their actions as PPAR ligands and GPR120 agonists, fatty acids and their metabolites can engage the histone acetylation machinery through more direct biochemical routes, a relationship recently reviewed comprehensively by Ediriweera, who catalogued short-, medium-, and long-chain fatty acids, including polyunsaturated species, as a structurally diverse class of natural histone deacetylase inhibitors capable of altering global and locus-specific histone acetylation independent of nuclear receptor engagement [15]. The short-chain fatty acid literature offers the best-resolved mechanistic precedent for this class of action: Thomas and Denu demonstrated that propionate and butyrate, rather than acting solely as classical competitive HDAC inhibitors, are converted intracellularly to their acyl-CoA thioester forms and directly activate the acetyltransferase p300, stimulating histone acetylation through allosteric autoactivation of the acetyltransferase itself, an unanticipated dual mechanism (deacetylase inhibition combined with acetyltransferase activation) that substantially increases net histone acetylation at target loci [16]. Although this specific biochemical characterization was performed with short-chain rather than long-chain n-3 fatty acids, it establishes a general biochemical principle, that fatty acid-derived acyl-CoA species can serve as direct allosteric or substrate-level regulators of chromatin-modifying enzymes, that is directly relevant to interpreting how EPA-CoA or DHA-CoA thioesters generated during fish oil metabolism might analogously engage HAT or HDAC activity in adipose tissue.

Receptor-mediated signaling provides a second, non-mutually-exclusive route from omega-3 fatty acids to altered chromatin state. Oh and colleagues identified GPR120 as a physiological omega-3 fatty acid receptor whose activation by DHA in macrophages and adipocytes produces broad anti-inflammatory and insulin-sensitizing effects by inhibiting TAB1-mediated activation of the TAK1 kinase complex and thereby suppressing both the NF-κB and c-Jun N-terminal kinase inflammatory signaling pathways [6]. Because NF-κB signaling recruits p300/CBP and other coactivators to inflammatory and adipogenic gene promoters, GPR120-mediated suppression of this pathway by DHA provides an indirect but biochemically plausible route by which n-3 PUFA could reduce histone acetylation at pro-inflammatory loci in adipose tissue without directly inhibiting or activating HAT or HDAC enzymes. Quesada-López and colleagues extended this receptor-level mechanism to thermogenic gene regulation, showing that GPR120 activation in brown and beige adipocytes stimulates the thermogenic transcriptional program and triggers release of the adipokine FGF21, linking omega-3 fatty acid sensing at the plasma membrane to downstream nuclear transcriptional and, by extension, chromatin-level events [7]. Considered alongside the direct nuclear receptor ligand and acyl-CoA-based mechanisms described above, the literature therefore supports at least three non-exclusive biochemical routes, direct enzyme modulation by fatty acid or acyl-CoA species, PPAR ligand-activated transcription, and GPR120-dependent suppression of coactivator-recruiting inflammatory signaling, through which

omega-3 fatty acids could plausibly converge on altered histone acetylation at adipogenic and adipokine gene loci.

Epigenetic Programming of Adipose Genes by Dietary Omega-3 Intake

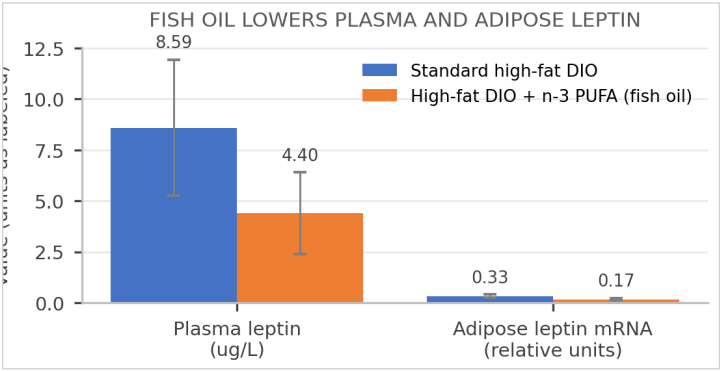
The clearest direct evidence that dietary omega-3 fatty acids alter histone acetylation at a specific, physiologically important adipose gene locus in vivo comes from Shen and colleagues, who compared diet-induced obese mice fed a standard high-fat diet with diet-induced obese mice whose high-fat diet was supplemented with fish oil. Plasma leptin concentration was significantly lower in the n-3 PUFA-supplemented obese mice (4.40 ± 2.00 micrograms per liter) than in the standard diet-induced obese group (8.59 ± 3.34 micrograms per liter), and adipose leptin messenger RNA levels were correspondingly reduced (0.17 ± 0.05 relative units versus 0.33 ± 0.07 relative units). Critically, this reduction in leptin expression was not accompanied by increased DNA methylation at the leptin promoter CpG island, which the same n-3 PUFA supplementation did not significantly alter; rather, fish oil supplementation significantly increased histone H3 acetylation at the leptin promoter while reducing the promoter binding of DNMT1, MBD2, and three separate class I and class II histone deacetylases, HDAC1, HDAC2, and HDAC6 [17]. This finding is mechanistically important because it demonstrates, in adipose tissue rather than a cultured cell line, that dietary n-3 PUFA can produce a locus-specific increase in histone acetylation accompanied by reduced HDAC occupancy, and that this histone-level mechanism, rather than DNA methylation, appears to be the operative epigenetic route by which fish oil lowers leptin expression in this model.

This adipose-tissue-level finding is consistent with, and helps to mechanistically anchor, the broader physiological literature on omega-3 fatty acids and adipose function. Marine-derived n-3 PUFA upregulate mitochondrial biogenesis and induce fatty-acid beta-oxidation in white adipose tissue partly through PPARα/PGC-1α-dependent transcription [18], and comprehensive reviews of the omega-3/adipose tissue literature describe consistent anti-inflammatory, adipokine-modulating, and browning-related actions of EPA and DHA across rodent and, to a more limited extent, human studies, while cautioning that supplementation dose, EPA:DHA ratio, treatment duration, and adipose depot examined vary considerably across the literature and limit direct cross-study comparison [19,20,21]. What remains comparatively underdeveloped is the direct extension of the Shen and colleagues histone-acetylation paradigm to other adipogenic loci, particularly Pparg and Cebpa themselves, and to human adipose tissue following controlled fish oil supplementation; the great majority of locus-resolved histone acetylation data in this field to date derive from a single rodent leptin-promoter study and from cultured 3T3-L1 preadipocytes rather than from human subcutaneous or visceral adipose biopsies. Closing this gap would require paired human supplementation trials combining chromatin immunoprecipitation at candidate adipogenic promoters with the more established transcriptional and lipid-accumulation endpoints already reported for DHA and EPA in cell culture.

Representative studies of omega-3 fatty acid effects on adipocyte differentiation and adipose epigenetic marks.

Study	Model	Fatty acid/dose	Principal finding
Kim et al. 2006	3T3-L1 preadipocytes	DHA, 25-200 uM	Dose-dependent inhibition of differentiation; apoptosis at 100-200 uM
Song et al. 2017	3T3-L1 adipocytes	DHA vs EPA, 50-200 uM	DHA raises adiponectin more than EPA; opposite effects on PPARγ Ser273 phosphorylation
Grigorova et al. 2025	3T3-L1, immature vs mature	DHA	-56% lipid accumulation (immature) vs +34% lipid mobilization (mature)
Shen et al. 2014	Diet-induced obese mice	Dietary fish oil (n-3 PUFA)	Increased leptin promoter H3 acetylation, reduced HDAC1/2/6 occupancy, lower plasma/adipose leptin
Fleckenstein-Elsen et al. 2016	Primary human adipocytes	EPA vs arachidonic acid	EPA selectively promotes brite phenotype and mitochondrial respiration

Fish oil (n-3 PUFA) supplementation of diet-induced obese mice lowers plasma leptin concentration and adipose leptin mRNA relative to standard diet-induced obese mice, a reduction attributed to increased histone H3 acetylation and reduced HDAC1/HDAC2/HDAC6 occupancy at the leptin promoter rather than to altered CpG methylation. Values (mean +/- SD) as reported by Shen et al. (2014).



Conclusion

Published biochemical, cell-culture, and rodent studies converge on a model in which fish oil-derived omega-3 fatty acids, principally EPA and DHA, modulate adipocyte differentiation through direct PPARγ ligand binding, phosphorylation-state regulation of PPARγ at serine 273, GPR120-dependent suppression of inflammatory coactivator recruitment, and, in at least one well-characterized adipose gene locus, a direct increase in histone H3 acetylation accompanied by reduced HDAC1, HDAC2, and HDAC6 promoter occupancy [10,9,8,6,17]. This histone-acetylation mechanism is biochemically consistent with, and plausibly reinforced by, independently documented roles for HDAC1/2, HDAC3, and SIRT1 as stage- and locus-specific regulators of the

core adipogenic and thermogenic transcriptional program [12,13,14], and with emerging evidence that fatty acid-derived acyl-CoA species can directly engage histone acetyltransferase and deacetylase enzymes independent of nuclear receptor signaling [16,15]. The principal limitation of the current evidence base is that direct, locus-resolved demonstration of omega-3-induced histone acetylation change in adipose tissue remains confined to a small number of rodent and cell-culture studies centered on a single well-characterized locus, leptin, with human data on omega-3-induced adipose histone acetylation essentially absent from the published literature. Future work pairing controlled human fish oil supplementation trials with chromatin immunoprecipitation profiling of PPARG, CEBPA, and adipokine promoters in paired subcutaneous adipose biopsies would allow the field to move from the current, mechanistically coherent but largely preclinical picture toward a directly validated account of nutritional epigenetic regulation of human adipocyte differentiation.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Kelly N conceived the review, conducted the literature search, and drafted the manuscript. Virtanen S contributed to the literature screening and technical framing and critically revised the manuscript for important intellectual content. Fischer J contributed additional context and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

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