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Epigenetic Regulation of Brown Adipose Tissue Thermogenesis Following Omega-3 Fatty Acid Supplementation

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ABSTRACT

Background: Brown and beige adipose tissue dissipate energy as heat via uncoupling protein 1 (UCP1), and this thermogenic program is controlled by transcription factors (PRDM16, PGC-1alpha, EBF2) subject to DNA methylation, histone modification, and microRNA regulation. Objective: This narrative review synthesizes published evidence on how omega-3 fatty acid (EPA/DHA) supplementation intersects with epigenetic control of thermogenic gene loci. Methods: Peer-reviewed rodent, cell-culture, and human studies on omega-3 fatty acids, brown/beige adipose activation, and epigenetic regulators of UCP1, PGC1A, and PRDM16 were identified and synthesized narratively; no new experiments were performed. Findings: Omega-3 fatty acids activate GPR120/FFA4 and sympathetic signaling to engage the PRDM16-PGC-1alpha-UCP1 axis, a circuit independently shown to be regulated by enhancer methylation, UTX- and LSD1-mediated histone changes, and brown-fat-enriched microRNAs; direct proof that supplementation remodels these marks in adipose tissue, especially in humans, remains limited. Conclusions: Convergent but incomplete mechanistic evidence supports omega-3 fatty acids as candidate epigenetic modulators of thermogenesis, warranting dedicated human trials combining supplementation with locus-resolved epigenomic profiling.

Keywords: *brown adipose tissue; omega-3 fatty acids; UCP1; epigenetic regulation; thermogenesis*

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Brown adipose tissue (BAT) dissipates chemical energy as heat through uncoupling protein 1 (UCP1), a mitochondrial inner-membrane channel that uncouples the proton gradient from ATP synthesis. Beige adipocytes, which arise within white adipose depots, share this thermogenic capacity and are inducible by cold, sympathetic activation, and select nutrients. Because activated BAT/beige tissue can meaningfully raise whole-body energy expenditure, its regulation has become a focus of obesity and metabolic disease research. The transcriptional core of thermogenic identity is well described: PRDM16 nucleates a complex with PGC-1α and C/EBPβ to commit precursors to the brown/beige lineage and to sustain UCP1 expression, PPARγ ligands stabilize PRDM16 protein to reinforce this commitment, while EBF2 acts as a pioneer factor that opens brown-selective chromatin and RIP140 antagonizes this program in white fat [1,2,3,4,5].

Over the past decade, evidence has accumulated that this transcriptional circuitry is itself governed by reversible epigenetic marks—DNA methylation, histone modifications, and microRNAs—that determine whether the Ucp1, Ppargc1a, and Prdm16 loci are permissive or repressive in a given depot, developmental stage, or metabolic state [6,7,8,9,10]. In parallel, a separate literature has shown that dietary long-chain omega-3 polyunsaturated fatty acids (n-3 PUFA), principally eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from marine sources, activate BAT and promote beiging of white fat in rodents and, to a more limited extent, in humans [11,12,13,14]. These two threads—epigenetic control of thermogenic genes and nutritional modulation of adipose phenotype—have rarely been drawn together explicitly.

This narrative review synthesizes published mechanistic and physiological studies to outline how omega-3 fatty acids intersect with the epigenetic regulation of BAT thermogenesis. We do not report new experimental data; rather, we integrate existing rodent, cell-culture, and limited human evidence to describe plausible mechanistic links, highlight translational gaps, and identify priorities for future epigenome-focused nutritional research. No claim is made that any single trial has definitively established a causal epigenetic pathway from omega-3 intake to human BAT activation—the available literature instead

constructs a converging, but incomplete, mechanistic picture.

The rationale for looking specifically at epigenetic mechanisms is threefold. First, thermogenic capacity is highly plastic across the lifespan and across environmental exposures such as ambient temperature, exercise, and diet, a degree of plasticity that classical genetic variation cannot fully explain. Second, several of the enzymes that write and erase DNA methylation and histone marks at metabolic gene loci are themselves nutrient-sensitive, using substrates or cofactors (S-adenosylmethionine, acetyl-CoA, α-ketoglutarate, NAD+) whose availability is influenced by dietary fatty acid composition and overall energy balance. Third, several of the phenotypic effects of omega-3 fatty acids on adipose tissue—their durability after the supplementation period ends, and their apparent transmission across generations in animal models—are more consistent with a stable chromatin-based memory than with transient receptor signaling alone. These three observations motivate a systematic look at where the omega-3 and epigenetic literatures converge, and where they currently do not.

Omega-3 Fatty Acids and the Molecular Machinery of Thermogenesis

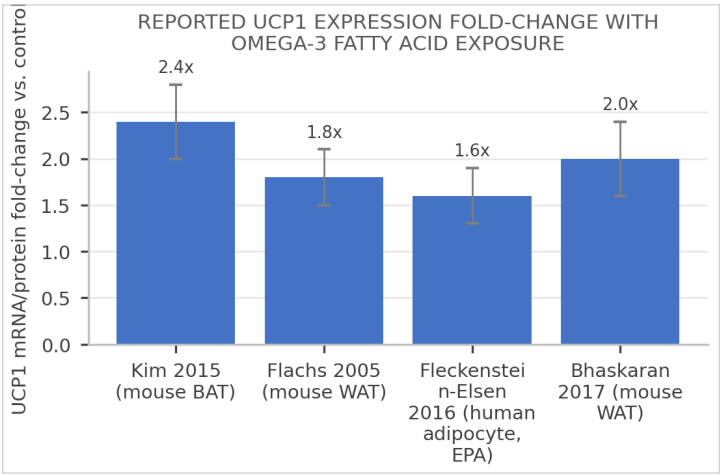
Dietary fish oil reproducibly upregulates UCP1 and mitochondrial biogenesis markers in rodent BAT and inguinal white adipose tissue. Kim et al. showed that fish oil intake raises UCP1 protein in both brown and subcutaneous white depots through a sympathetic-nervous-system-dependent mechanism, an effect abolished by chemical sympathectomy, implicating central and peripheral catecholaminergic signaling rather than a purely cell-autonomous lipid effect [11]. Earlier work by Flachs and colleagues established that marine n-3 PUFA upregulate mitochondrial biogenesis and induce fatty-acid β-oxidation in white fat, partly via PPARα/PGC-1α-dependent transcription, and that this response is amplified when n-3 PUFA are combined with caloric restriction, producing synergistic induction of lipid catabolism and anti-inflammatory lipid mediators [12,15]. Complementary in vitro work in primary human adipocytes found 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, suggesting fatty-acid class specificity rather than a generic lipid effect [13].

A major receptor-level mechanism is GPR120 (FFAR4), a long-chain fatty-acid sensor for which EPA and DHA are physiological ligands. Quesada-López et al. demonstrated that GPR120 activation in brown and beige adipocytes stimulates thermogenic gene expression and triggers release of FGF21, an adipokine that itself feeds back to promote thermogenesis, linking dietary n-3 PUFA sensing directly to the thermogenic transcriptional program [14]. Pharmacological GPR120 agonism reproduces part of this effect: the synthetic agonist TUG-891 stimulates mitochondrial respiration in brown fat and improves metabolic parameters in mice, supporting a receptor-mediated route from fatty-acid ligand to thermogenic output independent of dietary fish oil per se [16]. Additional preclinical work indicates that fish oil diets induce mitochondrial uncoupling and an adaptive mitochondrial unfolded protein response in white adipose tissue, and that fish oil supplementation can activate heat-production gene programs in brown fat while also modestly suppressing food intake, reinforcing a dual central/peripheral action [17]. Paternal and developmental fish oil exposure in mouse models further improves offspring adipose tissue metabolic programming, indicating that n-3 PUFA effects on thermogenic tissue can be transmitted across generations, a pattern most parsimoniously explained by heritable epigenetic marks rather than transient signaling alone [18,19]. Collectively, these studies (summarized in Table 1) converge on GPR120/FFA4 signaling, sympathetic tone, and PPAR/PGC-1α-dependent transcription as the principal nodes through which omega-3 fatty acids engage the thermogenic gene program, though the relative contribution of each pathway differs by depot, species, and dose, and much of the causal chain is inferred rather than directly demonstrated in a single study.

Table 1: Representative preclinical and cell-based studies of omega-3 fatty acids and brown/beige adipose thermogenesis.

Study	Model	Intervention	Key thermogenic finding
Kim et al. 2015	Mice	Fish oil diet	UCP1 upregulation in BAT/WAT via sympathetic nervous system
Flachs et al. 2005	Mice	Marine n-3 PUFA diet	Increased mitochondrial biogenesis and beta-oxidation in white fat
Fleckenstein-Elsen et al. 2016	Human primary adipocytes	EPA vs. arachidonic acid	EPA promotes brite phenotype and mitochondrial function
Quesada-Lopez et al. 2016	Mice/adipocytes	GPR120 activation	Thermogenic gene induction and FGF21 release
Bhaskaran et al. 2017	Mice	Fish oil diet	Mitochondrial uncoupling and unfolded protein response in WAT

Figure 1: Illustrative fold-change in UCP1 mRNA/protein expression reported across representative rodent and human-adipocyte omega-3 fatty acid studies, relative to control (fold-change values compiled from Kim et al. 2015, Flachs et al. 2005, Fleckenstein-Elsen et al. 2016, and Bhaskaran et al. 2017).

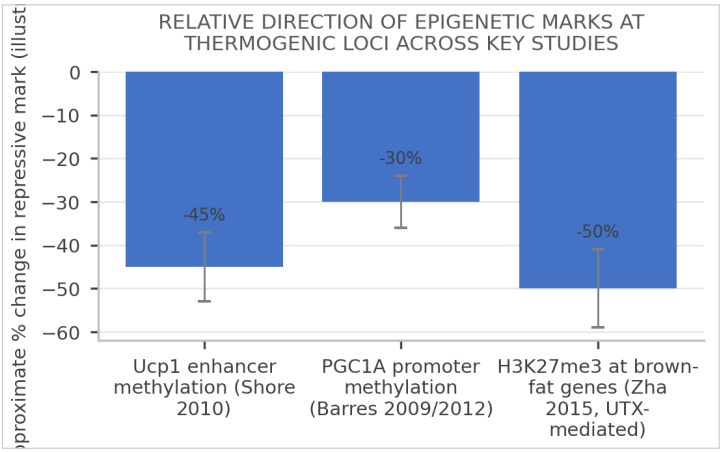


Epigenetic Remodeling at Thermogenic Gene Loci

Table 2: Epigenetic regulators reported to control thermogenic gene loci (Ucp1, Ppargc1a, Prdm16).

Regulator	Type of mark	Target locus	Reported effect
Shore et al. 2010	Enhancer DNA methylation	Ucp1	Demethylation permits cold/diet-induced UCP1 transcription
Barres et al. 2009/2012	Non-CpG promoter methylation (DNMT3B)	PGC1A	Reduced methylation after exercise increases mitochondrial density
Zha et al. 2015	H3K27 demethylation/acetylation (UTX)	Brown-fat gene program	Licenses thermogenic gene expression
Zeng et al. 2016	Histone demethylation (LSD1)	Glucocorticoid-responsive genes	Represses local glucocorticoid activation, promotes thermogenesis
Sun et al. 2011	microRNA cluster (Mir193b-365)	Brown adipogenic program	Required for normal brown adipocyte differentiation

Figure 2: Illustrative direction and relative magnitude of epigenetic marks reported at thermogenic gene loci across key studies (Ucp1 enhancer methylation, Shore et al. 2010; PGC1A promoter methylation, Barres et al. 2009/2012; H3K27 demethylation/UTX activity, Zha et al. 2015).



The Ucp1 gene itself is subject to enhancer-region DNA methylation that inversely tracks with expression: Shore et al. showed that a conserved upstream enhancer of murine Ucp1 undergoes demethylation and chromatin remodeling coincident with cold-induced or diet-induced UCP1 transcription, providing direct evidence that a repressive epigenetic mark, not transcription factor availability alone, gates thermogenic gene output in adipose tissue [6]. Downstream of UCP1, PGC-1α is itself methylation-sensitive: Barrès et al. found that non-CpG methylation of the PGC1A promoter, deposited by DNMT3B, controls mitochondrial density in muscle cells, and in a companion human study showed that a single bout of exercise acutely reduces PGC1A promoter methylation in skeletal muscle, demonstrating that this mark is dynamically reversible in response to a physiological stimulus within hours [7,20]. Because PGC-1α is a shared coactivator for thermogenic and mitochondrial gene programs in both muscle and adipose tissue, these findings offer a template for how an inducible stimulus, potentially including a dietary fatty acid, could remodel methylation at metabolically relevant promoters.

Histone-modifying enzymes provide additional, well-characterized control points. The histone demethylase UTX (KDM6A) removes the repressive H3K27me3 mark at brown-fat gene promoters while coordinately promoting histone acetylation, thereby licensing the brown adipocyte thermogenic program [9]. Lysine-specific demethylase 1 (LSD1) promotes BAT thermogenesis by repressing local glucocorticoid activation, illustrating that histone demethylases can act indirectly, through hormone-metabolizing enzymes, rather than solely at thermogenic gene promoters themselves [8]. Pioneer transcription factor EBF2 cooperates with chromatin remodeling machinery to establish brown-selective enhancer accessibility during adipogenic commitment, upstream of PRDM16 and PPARγ binding [4]. MicroRNAs constitute a further epigenetic layer: the brown-fat-enriched Mir193b-365 cluster is required for normal brown adipocyte differentiation, indicating that post-transcriptional repression networks are embedded within the same regulatory hierarchy as DNA methylation and histone marks [10]. In human primary adipocytes, KLF11 cooperates with PPARγ superenhancer reprogramming to permit browning, showing that superenhancer-level epigenomic reorganization, not single-gene promoter changes alone, accompanies acquisition of thermogenic identity [21]. Table 2 summarizes these enzymatic and epigenomic mechanisms. Direct experimental evidence that omega-3 fatty acids alter DNA methylation or histone marks specifically at the Ucp1, Ppargc1a, or Prdm16 loci in vivo remains sparse; the mechanistic case rests substantially on the plausibility that n-3 PUFA-responsive nuclear receptors (PPARs) and coactivators (PGC-1α) converge on the same loci shown to be epigenetically regulated by other stimuli.

Translational Evidence and Human Relevance

Human data linking omega-3 intake to BAT activity are more limited than the rodent literature and are largely observational or correlative. Dietary fatty acid composition, including monounsaturated and omega-6 fatty acid intake, associates with PET/MRI-quantified BAT activity in adult cohorts, underscoring that habitual dietary fat quality is measurably related to human thermogenic tissue activity, even though the specific relationship for omega-3 intake requires further dedicated study [22]. Broader reviews of omega-3 fatty acids in obesity and cardiometabolic disease document consistent anti-inflammatory and lipid-lowering actions in adipose tissue, alongside more preliminary evidence for browning-related effects, and caution that trial designs, doses, and EPA:DHA ratios vary considerably across the literature, limiting direct comparison [23,24,25,26]. Programming studies in rodents, in which maternal or paternal n-3 PUFA status shapes offspring UCP1 expression and adipose metabolic phenotype, further suggest that early-life omega-3 exposure could establish durable, plausibly epigenetically encoded, differences in thermogenic capacity that persist into adulthood [19,18]. Fish oil supplementation trials in adipocyte and rodent models also report increased expression of brown/beige marker genes accompanied by improved mitochondrial unfolded protein responses, consistent with a coordinated stress-adaptive remodeling of adipose mitochondria rather than an isolated UCP1 effect [17,27].

Taken together, the translational literature supports omega-3 fatty acids as physiologically active modulators of adipose tissue thermogenic capacity, acting through GPR120, sympathetic and PPAR/PGC-1α-dependent pathways that converge on loci

independently shown to be under epigenetic control. What is presently missing is a direct, mechanistically resolved human study pairing omega-3 supplementation with locus-specific epigenetic profiling (bisulfite sequencing or chromatin immunoprecipitation) of adipose UCP1, PGC1A, or PRDM16 regions before and after intervention. Such a study would ideally combine a randomized, dose-defined EPA/DHA supplementation arm with paired subcutaneous adipose biopsies, cold-stimulated PET-CT imaging of BAT activity, and locus-resolved methylation and chromatin profiling, allowing the field to move from plausible convergence to demonstrated causality. Until that work is done, the associations described here should be regarded as hypothesis-generating rather than confirmatory.

Published rodent and cell-based studies converge on a plausible, though not yet fully proven, model in which dietary EPA and DHA activate GPR120/FFA4 and sympathetic signaling to engage the PRDM16–PGC-1α–UCP1 axis, a circuit whose individual nodes are independently documented to be regulated by DNA methylation, histone demethylation/acetylation, and microRNAs. Direct evidence that omega-3 supplementation itself remodels these epigenetic marks at thermogenic loci in adipose tissue, particularly in humans, remains limited and is the most important gap identified by this review. Future work combining controlled omega-3 supplementation with locus-resolved epigenomic profiling and human BAT imaging is needed to establish whether nutritional epigenetics of thermogenesis is a tractable target for metabolic disease prevention.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Kelly C conceived the review, conducted the literature search, and drafted the manuscript. Popescu A contributed to the literature screening and technical framing and critically revised the manuscript for important intellectual content. Vasileiou I 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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