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Why HMG-CoA reductase escapes feedback inhibition in hypercholesterolemia: A mechanistic hypothesis integrating metabolic, genetic and post-translational dysregulation

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Abstract

Cholesterol synthesis is physiologically constrained by negative feedback inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR). Paradoxically, many patients with familial or metabolic hypercholesterolemia exhibit persistently elevated hepatic HMGCR activity despite intracellular sterol accumulation. This conceptual hypothesis proposes that hypercholesterolemia represents a state of "metabolic feedback resistance," wherein the normal sterol-sensing and degradation machinery of HMGCR is disrupted by overlapping molecular defects.

We postulate that impaired function of the INSIG–SCAP–SREBP2 complex, post-translational stabilization of HMGCR due to AMPK inactivation and defective ubiquitination, and chronic endocrine drive from insulin and cytokines jointly uncouple cholesterol synthesis from sterol feedback. Furthermore, epigenetic activation and microRNA modulation (notably miR-33a/b) reinforce persistent expression of cholesterol synthesis genes. This integrated "feedback-escape" model predicts that HMGCR half-life, phosphorylation, and transcriptional activity remain elevated independent of sterol levels, explaining both hypercholesterolemia and partial statin resistance. Experimental validation using hepatocyte models, genetic manipulations of INSIG or AMPK, and human biopsy or biomarker studies could establish metabolic feedback resistance as a key pathogenic mechanism. Restoring feedback sensitivity through AMPK activation, INSIG stabilization, or E3-ligase modulation may represent a novel therapeutic strategy for dyslipidemia and metabolic disease.

Keywords: HMG-CoA reductase; Hypercholesterolemia; Feedback inhibition; SREBP2; INSIG; AMPK; Metabolic feedback resistance; Sterol sensing

1. Introduction

Cholesterol homeostasis depends on tightly coupled regulation of synthesis, uptake, and efflux. The rate-limiting enzyme 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) catalyzes the conversion of HMG-CoA to mevalonate, serving as a metabolic checkpoint in sterol biosynthesis [1, 2].

Under physiologic conditions, feedback inhibition by intracellular sterols downregulates HMGCR transcription via SREBP2, enhances its degradation via E3 ligases such as gp78 and TRC8, and promotes inhibitory phosphorylation through AMP-activated protein kinase (AMPK) [2,3, 4].

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However, in familial combined hyperlipidemia, obesity, insulin resistance, and type 2 diabetes, hepatic HMGCR activity remains abnormally elevated even under cholesterol-replete states [5, 6, 7]. This paradox implies a breakdown in sterol sensing and enzyme regulation.

Here, we hypothesize that these metabolic conditions represent a state of "metabolic feedback resistance" (MFR)—a systemic failure of sterol-sensing and feedback signaling across transcriptional, post-translational, and hormonal axes.

2. Mechanistic Background

2.1. Canonical Sterol Feedback Regulation

In healthy hepatocytes, low sterol levels cause SREBP2–SCAP translocation from the ER to the Golgi, where proteolytic cleavage releases transcriptionally active SREBP2 [1, 8].

When sterol levels rise, INSIG1/2 binds SCAP, retaining the complex in the ER and halting transcription of cholesterol biosynthetic genes [9]. Simultaneously, sterols induce ubiquitination of HMGCR via E3 ligases gp78 and TRC8, promoting proteasomal degradation [10, 11, 12].

AMPK phosphorylates HMGCR at Ser872 during energy stress, inactivating it [3,13, 14]. This multi-tiered regulation ensures cholesterol homeostasis through negative feedback at transcriptional, enzymatic, and hormonal levels.

2.2. Endocrine and Metabolic Modulation

Insulin and thyroid hormones activate SREBP1c and SREBP2, enhancing cholesterol synthesis [15]. Conversely, glucagon, leptin, and AMPK act as inhibitory counterbalances [16, 17, 18].

In obesity and diabetes, chronic hyperinsulinemia suppresses AMPK activity through mTORC1 activation, blunting inhibitory phosphorylation of HMGCR [19, 20, 21].

3. The Feedback-Escape Hypothesis

We hypothesize that hypercholesterolemia reflects "metabolic feedback resistance", wherein sterol accumulation fails to suppress HMGCR because of combined dysfunction in:

- Sterol sensing via INSIG–SCAP–SREBP2;
- Post-translational degradation via gp78/TRC8 or AMPK inactivation;
- Endocrine overstimulation by insulin and cytokines; and
- Epigenetic reprogramming via miR-33 and histone acetylation.

These mechanisms converge to decouple cholesterol synthesis from sterol feedback, producing persistent enzymatic activation.

4. Mechanistic Framework

4.1. Sterol-Sensing Dysfunction

INSIG–SCAP binding prevents SREBP2 activation during sterol sufficiency [8]. In insulin-resistant hepatocytes, ER stress and hyperinsulinemia reduce INSIG expression [22]. INSIG2 variants (rs7566605) have been linked to obesity and dyslipidemia [23]. The result is persistent SREBP2 nuclear localization despite high intracellular sterols [17].

4.2. Post-Translational Stabilization of HMGCR

ER stress induces oxidative modification of lysine residues on HMGCR, impairing ubiquitination and degradation [4, 24]. Downregulation of gp78 and TRC8 in fatty liver and obesity stabilizes HMGCR [25, 26].

AMPK suppression further prevents inhibitory phosphorylation at Ser872 [19, 20, 21], while phosphatase PP2A dephosphorylates and reactivates the enzyme [3].

4.3. Metabolic and Endocrine Drivers

Persistent insulin signaling activates SREBP1c and ChREBP, maintaining anabolic lipid synthesis [15, 27]. Inflammatory cytokines (IL-6, TNF-α) and adipokines further promote lipogenesis [28]. Leptin resistance suppresses AMPK activation [16], perpetuating feedback failure.

4.4. Epigenetic and microRNA Control

The SREBF2 gene encodes miR-33a, which suppresses cholesterol efflux transporters ABCA1 and ABCG1, trapping cholesterol intracellularly [29, 30].

Histone H3 acetylation at the HMGCR promoter enhances transcription even under sterol-replete conditions [31]. This establishes a "memory" of transcriptional activation, consolidating chronic dysregulation.

4.5. Integrated Model

These multi-level defects—sterol-sensing loss, AMPK inactivity, impaired degradation, endocrine overstimulation, and epigenetic fixation—create a "feedback-escape" state, where cholesterol synthesis proceeds independently of sterol levels.

5. Experimental Predictions and Validation

5.1. Cellular Signatures

- Cells in MFR should exhibit:
- Prolonged HMGCR half-life;
- Decreased Ser872 phosphorylation;
- Reduced ubiquitination;
- Elevated nuclear SREBP2;
- High miR-33a/b expression;
- Elevated cholesterol despite sterol excess.

5.2. In Vitro Models

HepG2 or HuH7 cells cultured in high-insulin, high-glucose medium with AMPK inhibition (Compound C) should show feedback escape. Restoration with AICAR or metformin should reinstate inhibitory phosphorylation [21, 32].

5.3. In Vivo Models

Diet-induced obese mice and db/db models should display elevated HMGCR protein, decreased AMPK phosphorylation, and nuclear SREBP2 accumulation [19, 20]. Liver-specific INSIG knockouts would further confirm sterol-sensing loss [9].

5.4. Human Studies

Liver biopsies from statin-resistant patients exhibit reduced INSIG1/2, elevated miR-33, and accumulation of sterol intermediates [6, 33]. Plasma miR-33a/b levels could serve as biomarkers for feedback resistance.

6. Clinical and Therapeutic Implications

6.1. Statin Resistance and LDL Persistence

Statins inhibit HMGCR catalysis but upregulate SREBP2, promoting compensatory synthesis [33]. This rebound suggests disrupted feedback loops underlie partial resistance.

6.2. Restoring Feedback Sensitivity

Therapeutic avenues include:

- AMPK activation (metformin, salicylate, AICAR) to re-establish phosphorylation control [18].
- E3 ligase modulation (gp78/TRC8 agonists) to restore degradation [12].

- INSIG stabilizers to enhance sterol sensing [22].
- Anti–miR-33 therapy or HDAC inhibitors to reprogram transcriptional feedback [30].

7. Alternative Explanations and Limitations

Alternative drivers may include increased acetyl-CoA flux, oxysterol-mediated LXR activation [34, 35], or compartmental ER cholesterol depletion stemming from disrupted intracellular cholesterol trafficking [36, 37, 38]. In vitro systems lack endocrine integration and may mask redundant compensatory mechanisms when single pathways are knocked out.

Highlights

- Hypercholesterolemia may involve "metabolic feedback resistance," where HMG-CoA reductase (HMGCR) escapes sterol-mediated inhibition.
- Convergent defects in INSIG–SREBP2 signaling, AMPK activity, and E3-ligase–mediated degradation impair cholesterol feedback control.
- Persistent SREBP2 activation and reduced HMGCR ubiquitination sustain cholesterol synthesis despite sterol overload.
- Chronic hyperinsulinemia, ER stress, and miR-33 overexpression reinforce sterol-sensing dysfunction.
- Targeting AMPK activation, INSIG stabilization, and HMGCR degradation may restore feedback sensitivity and improve statin response.

8. Conclusion

Hypercholesterolemia reflects not only excess synthesis or receptor failure but a loss of sterol-sensing fidelity. The proposed metabolic feedback resistance framework unites sterol-sensing dysfunction, post-translational stabilization, AMPK suppression, and epigenetic reinforcement into a cohesive mechanism explaining persistent HMGCR activation.

Restoring dynamic sterol feedback coupling may transform management of metabolic dyslipidemia and statin resistance.

Compliance with ethical standards

Disclosure of conflict of interest

The author declares no conflicts of interest.

Author Contribution (CRediT)

Tilahun Senbeto conceptualized the hypothesis, conducted the literature review, developed the mechanistic model, and wrote the full manuscript.

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