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THE ROLE OF THE ANGPTL3 PROTEIN IN LIPOPROTEIN METABOLISM AND ITS THERAPEUTIC POTENTIAL FOR DYSLIPIDEMIA

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Abstract: The ANGPTL3 protein plays a central role in lipid metabolism, regulating triglyceride (TG) and LDL-C levels, and is a promising therapeutic target for the management of refractory dyslipidemia and high cardiovascular risk. This study reviewed the literature on the mechanisms of action of ANGPTL3 and advances in therapies based on its inhibition, including agents such as evinacumab, antisense oligonucleotides (ASOs) and emerging technologies such as gene editing. Thirty articles published between 2020 and 2024 in PubMed were selected. The results indicate that ANGPTL3 inhibition significantly reduces LDL-C and TG levels, promoting benefits in high-risk populations, such as patients with homozygous familial hypercholesterolemia (HoFH). In addition, ANGPTL3-targeted vaccines and RNA-based therapies show promise in lipid modulation and cardiovascular risk reduction. However, challenges such as accessibility, high cost and lack of longitudinal studies limit their implementation on a large scale. It is concluded that ANGPTL3 inhibition represents an innovative and effective therapeutic approach with the potential to transform the management of severe dyslipidemia and reduce the burden of cardiovascular disease. Future studies should focus on cost-effective strategies, long-term validation and personalization of interventions, promoting greater accessibility and clinical impact.
Keywords: ANGPTL3, dyslipidemia, lipid metabolism, precision therapy

INTRODUCTION

Angiopoietin-like protein 3 (ANGPTL3) is an endogenous inhibitor of lipoprotein lipase (LPL), playing a central role in lipid metabolism by regulating plasma levels of triglycerides (TG) and low-density lipoproteins (LDL-C). Because of its action, ANGPTL3 stands out as a promising therapeutic target in the control of dyslipidemia, contributing to the reduction of cardiovascular risk and the prevention of serious complications, such as atherosclerosis (Chen *et al*., 2021).

Studies indicate that loss-of-function mutations in ANGPTL3 are associated with a more favourable lipid profile, characterized by reduced TG and LDL-C concentrations, as well as a lower risk of cardiovascular events (Kersten, 2021; Tomlinson *et al*., 2024). This evidence reinforces their clinical relevance and potential for innovative therapies.

Therapeutic advances, including the development of monoclonal antibodies and antisense oligonucleotides, have shown significant efficacy in reducing LDL-C and TG, especially in patients with dyslipidemias that are difficult to control, such as homozygous familial hypercholesterolemia and severe hypertriglyceridemia (Tokgozoglu; Libby, 2022; Tomlinson *et al*., 2024). According to Mohamed, Mansfield and Raal (2022), ANGPTL3 inhibition is emerging as an innovative approach to the management of refractory dyslipidemias, effectively reducing plasma lipids and cardiovascular risk. In addition, ANGPTL3 deficiency has been associated with positive regulation of hepatic metabolism, promoting greater efficiency in the clearance of TG-rich lipoproteins (Burks *et al*., 2024).

Despite advances, significant gaps remain in the complete understanding of the molecular mechanisms by which ANGPTL3 influences lipid metabolism, as well as its relationship with inherited disorders such as familial combined hyperlipidemia (FCHL). Genetic variants investigated by Bea *et al*. (2021) indicated that, although gain-of-function mutations have not been identified, ANGPTL3 plays a critical role in regulating lipid metabolism under complex conditions. Complementarily, Morelli, Chavez and Santulli (2020) highlight the ANGPTL3-4-8 trio as a central regulatory network in lipid metabolism, essential for modulating plasma lipid levels.

From a clinical point of view, the application of emerging technologies, such as gene editing and RNA-based therapies, offers new perspectives for the management of refractory dyslipidemia (Muscoli *et al*., 2022). Pharmacological inhibition of ANGPTL3 has been shown to be effective not only in reducing plasma lipids, but also in preventing the progression of atherosclerotic cardiovascular diseases (Chen *et al*., 2021). These therapeutic approaches represent a promising alternative, particularly in scenarios where traditional pharmacological options are limited or ineffective (Tomlinson *et al.,* 2024).

This study aims to analyze the regulatory role of ANGPTL3 in lipoprotein metabolism, exploring the mechanisms by which this protein influences plasma lipid levels and its impact on cardiovascular health. In addition, it seeks to discuss recent therapeutic advances, including the development of ANGPTL3 inhibitors and their implications for the management of dyslipidemia. The review will address aspects such as the molecular mechanisms of action of ANGPTL3, its genetic relevance and the clinical potential of emerging therapies in the context of refractory and high-risk dyslipidemias

METHODOLOGY

This is a literature review developed according to the criteria of the PVO strategy, which stands for: population or research problem, variables and outcome. This strategy was used to develop the research question "How does the ANGPTL3 protein influence lipoprotein metabolism and what are the therapeutic implications of its inhibition for the treatment of dyslipidemia?". The searches were carried out using the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) databases. The search terms were used in combination with the Boolean terms "**AND", "OR" or "NOT"** (mention which operators were used), using the following search strategy: ((ANGPTL3) OR (Angiopoietin-like Protein 3)) AND (dyslipidemia). From this search, **323** articles were found, which were then submitted to the selection criteria. The inclusion criteria were: articles in **English**; published between **2020** and **2024** and which addressed the themes proposed for this research, review-type studies, meta-analysis, observational studies, experimental studies, clinical case studies, qualitative research, quantitative research and descriptive studies. The exclusion criteria were: duplicate articles, articles available in abstract form, articles that did not directly address the proposal studied and articles that did not meet the other inclusion criteria. After applying the search strategy to the database, a total of **215** articles were found. After applying the inclusion and exclusion criteria, **30** articles were selected from the PubMed database to make up this study's collection.

DISCUSSION

The ANGPTL3 protein plays a central role in the regulation of lipid metabolism, directly influencing the levels of triglycerides, LDL--C and HDL-C. Its inhibition has been widely investigated as an innovative therapeutic approach in the management of severe and refractory dyslipidemia. According to Kim, Ginsberg and Choi (2022), agents such as evinacumab have shown significant efficacy in reducing LDL-C in patients with refractory hypercholesterolemia. This effect is supported by studies showing evinacumab's ability to lower lipid levels independently of the LDL receptor Sosnowska *et al*., 2022).

The therapeutic impact of ANGPTL3 inhibition transcends LDL-C reduction. Therapies such as evinacumab and vupanorsen offer substantial reductions in triglyceride and LDL-C levels, making them promising options for patients with refractory dyslipidemia (Kim; Kim, 2023). These benefits are especially relevant for populations at high cardiovascular risk, such as individuals with homozygous familial hypercholesterolemia (HoFH). According to Kosmas *et al*. (2022), evinacumab demonstrated high efficacy in reducing LDL-C (~50%) in patients with HoFH, including those with LDL receptor null mutations.

In addition, ANGPTL3 inhibition has been investigated in different population contexts. According to Ginsberg and Goldberg (2023), ANGPTL3 inhibition and its interaction with ANGPTL8 stand out as complementary strategies for modulating lipid metabolism in patients with mixed dyslipidemia. According to Moon, Kim and Choi (2022), the role of lipoprotein lipase (LPL), modulated by ANGPTL3, reinforces its relevance as a therapeutic target, promoting significant reductions in triglycerides.

Another important advance is in vaccines targeting ANGPTL3. For Fukami *et al*. (2021), these vaccines have shown a positive impact in experimental models, demonstrating reductions in LDL-C and triglycerides, as well as attenuation in the formation of atherosclerotic plaques. Similarly, Kaewkrasaesin *et al*. (2021) explored the associations between ANGPTL3, ANGPTL8 and lipid biomarkers, indicating that these targets may vary in efficacy depending on factors such as gender and obesity.

The emergence of RNA-based therapies, such as antisense oligonucleotides (ASOs) and siRNAs, offers a new perspective for the management of dyslipidemia. According to Kim and Choi (2022), these agents demonstrate robust efficacy in reducing lipid levels, while Makhmudova *et al.* (2024) point out that technologies such as siRNA offer additional benefits, such as greater durability and safety. These advances are reinforced by genetic studies. Landfors *et al*. (2024), reinforce that the reduction of ANGPTL3 is directly associated with lower cardiovascular risks and a more favorable lipid profile.

In addition, evinacumab has been shown to be effective in specific clinical studies. According to Reeskamp *et al*. (2021), the drug accelerates the clearance of LDL apoB, promoting significant reductions in LDL-C, even in patients with HoFH. Vaccines against ANGPTL3 remain under investigation as complementary strategies in the management of refractory dyslipidemia, according to Fukami *et al*. (2021).

In addition, recent studies have explored the impact of ANGPTL3 inhibition in different populations and contexts. (2021), ANGPTL3 and ANGPTL8 levels correlate specifically with atherogenic lipid biomarkers, varying with gender and obesity status. These findings reinforce the need for personalized therapeutic strategies.

Another relevant aspect is the impact of emerging therapies on long-term cardiovascular risk. Ward, Chan and Watts (2022) point out that the combination of ANGPTL3 inhibitors with other therapeutic targets, such as apoC-III, provides additional benefits in the management of severe hypertriglyceridemia, representing a multifaceted approach to reducing the risk of metabolic complications.

In addition, gene editing has emerged as an innovative solution. According to Bellosta *et al*. (2023), technologies such as CRISPR-Cas9 offer transformative potential for treating severe genetic conditions such as HoFH. These advances are complemented by RNA-based therapies such as Inclisiran, which demonstrate sustained efficacy and favorable safety, according to Macchi *et al.* (2019).

According to Dingman *et al.* (2024), evinacumab also stands out for promoting rapid reductions in LDL-C levels, with effects observed as early as the second week of treatment in patients with homozygous familial hypercholesterolemia. The efficacy of this therapy is particularly relevant in pediatric and young adult patients.

The impact of these therapies is also reflected in the context of accessibility and cost-effectiveness. Tromp, Stroes and Hovingh (2020) emphasize that cost-effectiveness analysis is essential to optimize the clinical impact of emerging technologies such as antisense oligonucleotides and siRNAs.

Finally, Mendelian randomization analyses reinforce the role of ANGPTL3 as a central therapeutic target. According to Landfors *et al*. (2024), genetic reduction of ANGPTL3 is associated with a lower incidence of cardiovascular disease, reinforcing the clinical validity of targeted therapies.

On the other hand, challenges related to accessibility and cost remain. Nurmohamed, Dallinga-Thie and Stroes (2020), warn that the high costs of these therapies may restrict their clinical application, reinforcing the im-

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portance of advances in cost-effectiveness. For Bellosta *et al.* (2023), gene editing, including CRISPR-Cas9, offers a potential solution for severe genetic conditions such as HoFH.

According to Rosenson (2021), ANGPTL3 inhibition with evinacumab offers an effective solution for reducing LDL-C levels, particularly in patients refractory to conventional therapies such as statins and PCSK9 inhibitors.

According to Landmesser *et al.* (2020), nucleic acid-based therapies, such as ASOs and siRNAs, have the potential to modulate specific therapeutic targets, such as ANGPTL3 and apoC-III, providing a precision approach to the treatment of dyslipidemia.

In short, ANGPTL3 inhibition has become a central approach in the management of complex dyslipidemias. Reviewed studies show its impact on reducing triglycerides, LDL-C and cardiovascular risk. However, challenges related to accessibility and long-term validation remain, requiring continuous efforts in research and innovation to overcome these limitations.

FINAL CONSIDERATIONS

The ANGPTL3 protein stands out as a central regulator of lipid metabolism, directly influencing triglyceride, LDL-C and HDL-C levels. This study reviewed the relevance of ANGPTL3 in the context of dyslipidemias, emphasizing its inhibition as a promising therapeutic approach for refractory and high cardiovascular risk conditions such as homozygous familial hypercholesterolemia (HoFH). Evidence indicates that agents such as evinacumab and antisense oligonucleotides (ASOs) are highly effective in reducing plasma lipids, demonstrating significant potential for improving metabolic and cardiovascular outcomes.

However, despite therapeutic advances, important challenges remain. The limited accessibility and high costs of new therapies restrict their large-scale clinical application, while the lack of robust longitudinal studies makes it difficult to validate their long-term efficacy and safety. In addition, factors such as inter-individual variability in therapeutic response and the need for personalized strategies reinforce the relevance of investigating the molecular and genetic mechanisms that regulate ANGPTL3.

Advances in emerging technologies, such as gene editing and RNA-based therapies, offer promising prospects for the management of severe dyslipidemia. Tools such as CRISPR-Cas9 and Inclisiran stand out for their potential to treat severe genetic conditions in a lasting and effective way. In addition, vaccines targeting ANGPTL3 are being investigated as alternatives to improve lipid control and mitigate cardiovascular risk.

Finally, ANGPTL3 inhibition has been consolidated as an innovative and multifaceted therapeutic approach for the management of dyslipidemia, with significant impacts on the reduction of plasma lipids and the risk of cardiovascular complications. Future research should prioritize cost-benefit optimization, long-term validation and personalization of interventions, enabling the widespread implementation of these strategies in clinical practice. This line of research has the potential to transform the treatment of dyslipidemia, contributing to improving quality of life and reducing the burden of cardiovascular disease in high-risk populations.

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