A Review on Inducing Omega-3 Fatty Acids in Cultured Meat through Fisheries and Plant Cells

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ABSTRACT

A ground-breaking answer to the moral and environmental problems with conventional cattle husbandry is provided by cultured meat. Replicating the nutritional profile of traditional meat, especially the addition of vital elements like omega-3 fatty acids, is a significant difficulty. Current research on techniques for enriching and generating omega-3 fatty acids in cultured meat is summarized in this review study. We look at tactics including using specialized scaffolds, adding precursor lipids or direct sources like microalgae to cell culture medium, and metabolically engineering cultured cells. Along with the difficulties associated with oxidative stability, flavor profile, and economic viability, we also go over the physiological and metabolic pathways that are involved. This study offers a thorough summary of the advancements and potential paths forward for producing omega-3-fortified cultured meat that is both commercially feasible and nutritionally superior by critically assessing these novel techniques.

INTRODUCTION

A significant challenge for the World Food Program (WFP) is to satisfy the increasing food requirements of the burgeoning population while maintaining nutritional integrity. It is projected that, by 2050, the global populace is anticipated to exceed 9 billion. The Food and Agricultural Organization (FAO) forecasts that approximately 70% more food will be necessary to cater to this growing demographic. The appetite for meat consumption remains robust, particularly in nations like India, China and Russia, due to its high protein content and nutritional benefits [6]. Globally, livestock accounts for 17% of calorie and 33% of protein intake. In developing nations, the livestock industry is growing rapidly, contributing 33% to GDP and continues to rise annually [19]. This sector poses challenges for both cattle and poultry farming as it necessitates extensive land, food, and water resources, which are frequently limited in numerous regions [7].

Cultured meat, popularly known as "lab-grown meat," which is cell-based, cultivated, and slaughter-free, requiring significantly fewer resources [19]. While it serves as a plant-derived source rich in protein, consumer perceptions are divided, as it mimics the taste of conventional meat [16]. Currently, alternative meat products made from soybeans, nuts, wheat and grains are available in the market [38]. This benefits those people who hesitant to alter their dietary preferences while prioritizing sustainability. On August 5, 2013, a cultured beef hamburger was introduced in London, touted as a high-quality protein alternative [4]. Various sectors face challenges related to the limited production of cultured meat and are actively seeking solutions to enhance this aspect. Research efforts are ongoing to innovate methods and techniques for cultured meat production [12].

In contemporary times, individuals are increasingly becoming enlightened and mindful about their physical and mental well-being, in contrast to earlier generations. The pursuit of preserving and enhancing skeletal muscle mass and strength through various means is gaining traction. Among these strategies, omega-3 supplements have gained attention for their ability to boost anabolic activity in the skeletal muscle. [4]. In our daily lives, we include various fat components in our diet, which are basically made up of fatty acids. The omega 3 fatty acids produced in some plant sources, such as flax seeds and canola oil, are different from those produced in animals and fisheries [41]. These fatty acids, often referred to as essential fatty acids or polyunsaturated fatty acids, contain a double bond situated three carbon atoms from the methyl end and cannot be produced by humans [1].

The three primary forms of omega-3 fatty acids include docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and alpha-linolenic acid (ALA). They are primarily found in fish and certain plant sources, playing a crucial role in mitigating various chronic diseases such as heart disease, diabetes, and cancer [1]. To meet the growing demand for EPA and DHA supplements, the aquaculture sector is under tremondous pressure. In response, several companies are pioneering a new approach within the cultured meat sector. They are innovating to incorporate omega-3 fatty acids directly into cultured meat products [1,46,26]. This narrative review outlines the cells that generate omega-3 fatty acids in seafood and plant life, are incorporated into cultured meat to ensure adequate levels of omega-3 fatty acids and other essential nutrients for human health.

1. Cultured Meat

1. 1. The Concept and Development of Cultured Meat

Cultured meat, or *in vitro* meat, offers a revolutionary approach to protein production by growing animal cells in a controlled bioreactor environment. This method, adapted from tissue engineering, allows for the precise cultivation of muscle tissue, reducing reliance on conventional livestock farming. It stands as a sustainable alternative with significant environmental benefits [44]. Studies show that cultured meat could reduce land use by up to 99%, water consumption by 82-96%, and energy use by 7-45%. Additionally, it could decrease greenhouse gas emissions by up to 96% by eliminating emissions from enteric fermentation and manure. Cultured meat also presents opportunities for nutritional enhancement, such as reducing saturated fats and incorporating beneficial compounds like omega-3 fatty acids [35].

1.2 Key Milestones in the Cultivated Meat Industry

The conceptualization of slaughter-free meat production, initially designated as "in vitro meat," emerged in the early 21st century. A seminal milestone occurred in 2013 when Dr. Mark Post (Maastricht University) unveiled the inaugural lab-cultivated burger, financed by Google co-founder Sergey Brin. This demonstration catalyzed investments from venture capitalists including Peter Thiel, spurring the founding of pioneering entities like Memphis Meats (2015) and Mosa Meat (2016) [43]. Early research prioritized myocyte proliferation, neglecting critical attributes such as lipid content, textural complexity, and scalable manufacturing. Subsequent innovations addressed these gaps through serum-free media formulations and advanced bioreactor designs.

Regulatory ambiguity initially impeded public adoption, compounded by consumer apprehensions regarding "lab-grown" products. Academic engagement, initially tentative, expanded as food science and synthetic biology disciplines recognized the field's potential [31]. Concurrently, nomenclature debates ("clean meat" vs. "cultured meat") reflected efforts to shape public perception [43]. Notably, governmental interest predates commercial ventures: NASA funded early cell-cultivation research for space missions, acknowledging the infeasibility of livestock in microgravity [45]. Technological refinements—including induced pluripotent stem cells (iPSCs), microcarriers, and biomaterial scaffolds—enhanced efficiency, enabling global startup proliferation across Israel, Europe, and Asia [5].

1.3 Manufacturing and Bioprocess Design for Cultured Meat

Cultured meat biosynthesis encompasses cell isolation, proliferation, tissue differentiation, and harvest. Two primary cell sources are employed: satellite cells (adult myogenic stem cells) and pluripotent stem cells (PSCs), encompassing both embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). Satellite cells reside within skeletal muscle niches (between sarcolemma and basal lamina), governing myofiber repair and hypertrophy whereas, PSCs exhibit broader differentiation plasticity, generating lineages from all three germ layers (ectoderm, mesoderm, endoderm) [15].

Cell line selection critically influences the organoleptic and nutritional properties of the end product. Variations in protein synthesis kinetics, lipid metabolism, and extracellular matrix deposition dictate flavor, texture, and nutrient density. To emulate conventional meat's complexity, co-culturing strategies integrate adipocytes with myocytes, replicating marbling and mouthfeel. While ESCs are well-characterized, iPSCs present ethical and practical advantages—they circumvent embryo destruction and enable patient-specific meat production. Tissue maturation relies on engineered scaffolds (providing structural templates), bioreactors (modulating hydrodynamic and nutrient conditions), and defined growth media. These components collectively simulate *in vivo* mechanochemical cues essential for organized tissue development [42].

1.4 Frontiers in Cultivated Meat Production (2022–2025)

3D bioprinting is a major advancement that allows precise placement of muscle and fat cells, creating a more realistic texture and flavor. This technique also helps overcome issues with blood vessel formation and connective tissue integration. New scaffold designs, like tendon-gel hybrids, are also being used to create stronger, more aligned muscle fibers [42]. The industry is moving from R&D to large-scale production, with companies like Aleph Farms, Believer Meats, and GOOD Meat leading the way. Meanwhile, countries are specializing in different aspects of the field, such as R&D (U.S.), biotechnology (Israel), regulation (Singapore) and public engagement (EU) [32].

2. Overview of Plant Species rich in omega-3 fatty acids

Plant-based sources are a sustainable alternative to marine sources for omega-3 fatty acids, which are vital for human health. Key sources rich in alpha-linolenic acid (ALA) include flaxseed and chia seeds, with contents reaching up to 60.4% and 65% ALA, respectively [9]. Other plants like *Camelina sativa* and garden cress also provide significant amounts of ALA. Some plants from the *Echium* genus contain stearidonic acid (SDA), which the body converts to EPA more efficiently than ALA. For a direct source of DHA and EPA, both algal oil and genetically modified soybean oil are promising vegan alternatives [20]. The specific omega-3 content and composition in these plants can be influenced by external factors like climate, soil quality, and genotype. Additionally, certain oils, like garden cress, offer a balanced fatty acid ratio that enhances nutritional value and oxidative stability [13].

2.1 Genetic and Enzymatic Pathways of Omega-3 Biosynthesis in Plants

Fatty acid biosynthesis in plants begins in plastids with the conversion of acetyl-CoA into saturated fatty acids. Omega-3 fatty acids like alpha-linolenic acid (ALA) are then synthesized from linoleic acid via specific desaturase enzymes (*FAD7/FAD8* or *FAD3*). While plants don't naturally produce long-chain omega-3s like EPA and DHA, genetic engineering with enzymes from marine microbes has enabled their production [27]. The process involves two pathways: a prokaryotic one in plastids and a eukaryotic one in the endoplasmic reticulum. This synthesis is facilitated by an acyl editing pathway, which allows for rapid fatty acid exchange and efficient desaturation [2]. The major steps involved in this process are,

- Primarily desaturation takes place in which, conversion of stearic acid to oleic acid is carried out by an enzyme called Stearoyl-ACPAcyl, editing enzymes like LPCAT to help direct nascent fatty acids into desaturation cycles in the endoplasmic reticulum.
- GPAT9 and ATS1 (glycerol-3-phosphate acyltransferases) help in controlling the entry of acyl groups into the eukaryotic and prokaryotic pathways.
- FDA3 overexpression in transgenic plants increases Omega-3 fatty acid content (ALA) in seeds without compromising overall lipid yield. [37]

Genetic engineering is used to enhance long-chain omega-3 fatty acid production in oilseeds like Camelina by introducing genes for key enzymes such as delta-6-desaturase and delta-5-desaturase [24]. Environmental factors like cold and salt **stress** can also upregulate omega-3 desaturase genes (*FAD3*, *FAD8*), increasing the plant's stress resilience. Furthermore, light and temperature can modulate this biosynthesis through phytochrome-related transcription factors. The master transcription factor WRI1 (WRINKLED1) plays a crucial role in activating genes involved in both glycolysis and fatty acid synthesis [27].

2.2 Genetically Engineering Oilseed Crops for Long-Chain Omega-3 Production

The genetically modified species are introduced to increase the yield and enrich the nutritional value of the product. Genetically modified soybeans have been designed to produce stearidonic acid (SDA), which converts to EPA more efficiently than ALA [37]. SDA-enriched oil from modified crops shows higher oxidative stability, and these genetically engineered oils can easily be incorporated into foods compared to ALA-rich oils [36,29]. The crops like Camelina sativa have been bioengineered to synthesise EPA/DHA directly in seeds, which is the best alternative for fish oil; it is economically friendly compared to fish oil. The methods, like transgenic hosts in species like microalgae, can coproduce valuable bioactive compounds along with omega-3 fatty acids, it also maintains a low ecological footprint, and it doesn't require arable land. [39,3].

3. Overview of Omega-3 Fatty Acids in Animals and Fisheries

Omega-3 Fatty Acids can predominantly be found in animals and fish. The widely accessible source of Omega-3 Fatty Acids is Red Meat (defined as the muscle meat of beef, pork, lamb, goat, and a few other mammals) [17]. Several factors influence omega-3 fatty acid accumulation in animals, including environment, species, and diet. Among these, diet is the most critical, especially for animals raised for red meat. Pasture- and forage-based feeding, where cattle graze on cultivated pastures or natural ranges, is a primary method that supports the animals' natural well-being and enhances omega-3 content [24]. The quality of produce, such as milk and meat, from animals grown in their natural habitat will provide higher-quality products compared to those fed low-quality forages or formulated feeds [17].

Grain-fed and feedlot diets are common sources of n-6 PUFA, while pasture and forage diets provide abundant n-3 PUFA in livestock. Besides diet, genetics and growth also influence FA synthesis. [21,33]. An animal's fatty acid profile, including n-3 and n-6 PUFA accumulation, is directly influenced by its diet, reflecting dependence on plants. Modern agriculture and food processing have altered n-3 and n-6 PUFA levels in crops, affecting the fatty acid content of animals that consume them [11].

3.1. The Ruminant's Remix: Hacking Livestock Lipid Metabolism

Lipids consumed by livestock contribute to tissue integrity, structure, energy supply, and recognition systems. Livestock are classified as ruminants or monogastrics based on their digestive systems and feeding habits. Ruminant diets typically contain 1–4% fat, but lipid supplementation above 5–6% dry matter can negatively affect rumen function, especially carbohydrate digestion. However, it is significant not to forget the fact that these lipid supplements can also provide a few advantages to the ruminant. Few of those advantages are,

(i) reduction in methane into the environment during the degradation of high fibrous diet, facilitation of passage for dietary lipid from rumen to small intestine for absorption,

(ii) prevention of biohydrogenation of lipids and

(iii) redirection of dietary energy that is usually expelled out in methane emission and so on.

Unlike monogastric animals, where the liver plays a primary role in fatty acid (FA) synthesis, adipose tissue is the major contributor to FA synthesis in ruminants [21]. Figure 1 flowchart illustrates the reactions involved in the biosynthesis of EPA, DPA, and DHA.

3.1.1. Reactions involved in the biosynthesis of EPA, DPA and DHA

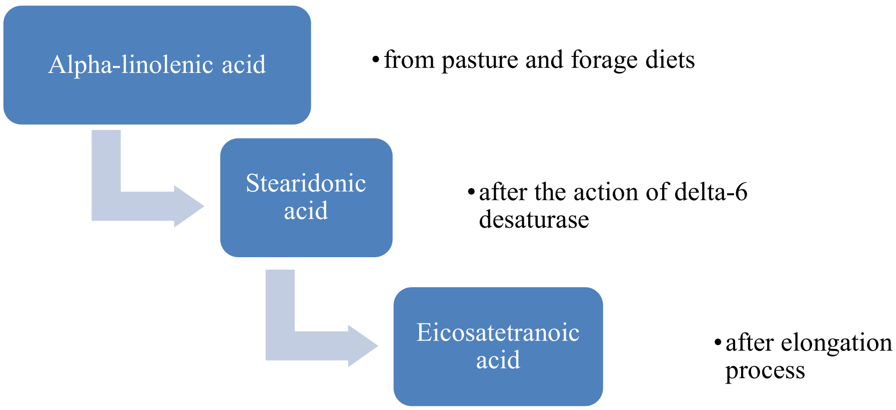

Fig. 1.1 Conversion of ALA into Eicosatetranoic acid

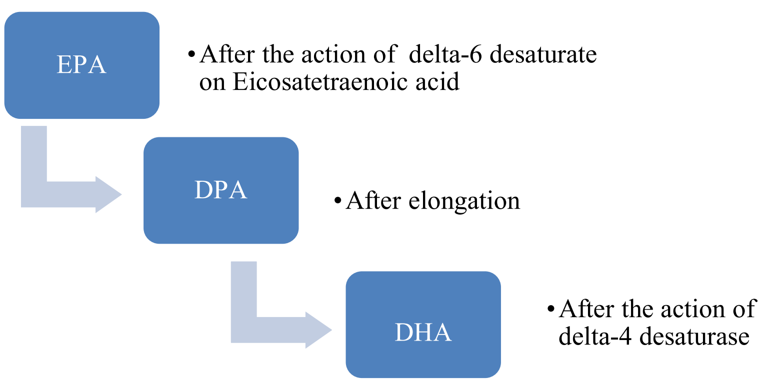

Fig.1.2 Conversion of EPA to DHA

Fig 1. A clear and concise flow chart that explains the process involved in the conversion of ALA into DHA.

Vegetable oils, or marine-based EPA and DHA to support omega-3 synthesis. However, ALA conversion to long-chain n-3 fatty acids is slow and limited by competition with LA for the same enzymes. High dietary intake of ALA or LA affects conversion efficiency, but long-term or high-dose feeding of ALA-rich diets like flaxseed or canola can increase EPA, DPA, and DHA in ruminant muscle [28].

Mammals can convert ALA to LCPUFAs like EPA, DPA, and DHA via desaturase- and elongase-mediated reactions.[23] Figure 1 gives a summarized flow chart of the conversion of ALA into DHA [8].

3.1.2. Factors that affect the accumulation of omega-3 and omega-6 FA in the meat of ruminants

Modern agricultural practices and large-scale livestock production have led to reduced n-3 PUFA and increased n-6 PUFA levels in meat. These levels are influenced not only by diet but also by dietary supplements, lipid types, enzyme competition, antioxidant and carotenoid content in muscle, and the presence of phytonutrients and secondary metabolites [34].

3.2 Omega-3 FAs in fisheries

A common misconception is that animals are the sole source of omega-3 fatty acids. In reality, n-3 FAs, particularly EPA and DHA, are abundant in aquatic sources like fish and fish oils. However, fish do not synthesize these fatty acids themselves; they accumulate them through their diet, primarily from microalgae. As primary producers in aquatic ecosystems, microalgae provide the foundational omega-3 fatty acids that move through trophic levels, highlighting that both terrestrial animals and fish ultimately rely on plants for these essential nutrients [22]. These essential FAs are not exclusively present in finned fishes. It is also available in other marine organisms. A recent study has found that omega-3 fatty acids are found in the eggs of the Red King Crab [25].

3.2.1. Microalgae's Metabolic Makeover: A Fish's Guide to Fatty Acid Conversion

The crucial process of hydrolysis of dietary lipids occurs in the intestinal lumen of the fish, where enzymatic processes (enzymatic breakdown) transform the complex dietary fats into simpler forms. The simple molecules are onoglycerides and free fatty acids (FFAs). Successively, these products get incorporated with bile salts and result in the formation of special structures called micelles, which are essential for the transport of hydrophobic fat molecules through the aqueous environment of the digestive tract [18]

After micelle formation, monoglycerides and free fatty acids (FFAs) are absorbed by enterocytes, the small intestine cells responsible for about 95% of lipid absorption. Inside enterocytes, FFAs are re-esterified and packaged into large lipoprotein particles called chylomicrons. These chylomicrons transport dietary fats from the intestine to the lymphatic system, which then drains into the bloodstream [47]. Lipids travel through the lymphatic system, passing the liver where initial transfer from chylomicrons occurs, enabling direct delivery to peripheral tissues. Once in the bloodstream, lipoproteins circulate throughout the fish's body for metabolism, such as oxidation or storage in adipose tissue. DHA is particularly important, accumulating in tissues that require it for optimal function [22].

The understanding of the complex conversion of n-3 FAs is vital for any type of research done related to cultured meat. During the experiments done for the fortification of n-3 FAs in cultured meat, a proper knowledge of the enzymatic actions involved in the conversion of DPA to DHA can help in choosing the optimal source for the extraction of suitable n-3 FAs. This ensures that the cultured meat can provide a compatible environment for the accumulation of omega-3 fatty acids.

4. Nutritional Fortification of Cultured Meat with Omega-3 Fatty Acids

Induction of omega-3 fatty acids in cultured meat involves deliberate modification of cell culture conditions and gene or metabolic pathway for inducing the production of such healthy fats. One of the effective methods is to produce precursors for omega-3 fatty acids like alpha-linolenic acid (ALA) or direct sources of omega-3 like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) through microbial sources like microalgae or flaxseed oil [25]. Alternatively, the biosynthesis genes of omega-3-can be transduced mostly found in human sea animals to animal muscle or fat stem cells and, therefore, endogenous synthesis is permitted to take place during tissue development. Bioengineered adipogenic cells co-cultured again with the final cultured meat product lipid profile can improve final product lipid profile. Such methods are aimed at improving the nutritional content of cultured meat to render it nearer the health impact of fish and other food products that are sources of omega-3 [18].

4.1 Strategies for Omega-3 Fatty Acid Biosynthesis and Enrichment

Firstly, cell line selection selects cell lines that naturally produce omega-3 fatty acids, but it can also convert precursor fatty acids into omega-3s. Adding omega-3 fatty acids or their precursors, such as alpha-linolenic acid, to the cell culture media is known as media supplementation. Genetically modified cells are added to the biosynthesis pathway to overexpress the enzymes involved in the manufacture of omega-3 fatty acids [47]. When it comes to metabolic engineering, there are a number of ways to introduce omega-3 fatty acids into cultured meat, including medium modification, lipid supplementation, and co-culturing with adipocytes. All the methods are used to increase the omega-3 fatty acid content mainly EPA and DHA which are typically absent or has low amount in traditional mammalian muscle tissue [50].

4.1.1 METABOLIC ENGINEERING

These are the genes (like desatutrase and elongadse genes) that synthesize omega-3 fatty acids into the DNA of animal muscle or into its fat precursor. The genes involved in this come from marine species or algae that naturally make DHA and EPA. Long-chain omega-3 fatty acids are subsequently formed by covering these genetically altered cells with simpler fatty acids. CRISPR/Cas9 and viral vectors are frequently utilized for steady gene integration during cell development. During the process of cell growth CRISPR/Cas9 and viral vectors are often used for stable gene integeration [10].

4.1.2 Lipid Supplementation and Media Optimization

This is another technique that includes direct supplies of EPA and DHA from vegetable or algae oils, or the inclusion of precursors to omega-3 fatty acids, such as alpha-linolenic acid (ALA). These fatty acids are incorporated by the cells and become part of their intracellular lipid deposits or membrane. Omega-3 uptake and retention can also be enhanced by optimizing the media's concentration of growth factors, fatty acid transport proteins, and lipid-storage molecules. Meat with enhanced omega-3 profiles may result from combining this with a specially designed lipid-dense diet for differentiated cells in culture [40].

4.1.3 Co-culture with Engineered Adipocytes

The more recent technique involves co-culturing muscle cells with adipogenic stem cells that have been modified to synthesize or accumulate higher amounts of omega-3 fatty acids. This allows for precise deposition of health-promoting lipids and mimics the natural marbling found in meat. Researchers can engineer the final meat composition of the grown meat to replicate traditional meat with better functional features by controlling the differentiation lineages and ratio of muscle and fat cells. The addition of omega-3 fatty acids to cultured meat provides a great nutritional and health benefit, making it a very promising advancement in food technology [48].

Traditional animal meals lack omega-3 fatty acids, particularly EPA and DHA, which are essential for neurological function, cardiovascular disease prevention, and inflammation reduction. Companies may produce a better-fed, healthier protein product that is beneficial for both brain development and cardiovascular health by incorporating these healthy fats into cultured beef. This is especially helpful for populations with limited omega-3 dietary intake from vegetables or seafood. Cultured beef enriched with omega-3 is also utilized to lessen the usage of overfished sea species, which can be beneficial for the environment. For the majority of people, adding omega-3 to cultured beef raises its nutritional value and advances global sustainability and health goals [49].

4.2 Exogenous Supplementation and Delivery Methods

There are several biological and technological obstacles to the induction of omega-3 fatty acids in cell-cultured beef. One of these is that because mammalian cells lack the enzymes required for desaturation and elongation, their natural capacity to produce long-chain omega-3s, such as EPA and DHA, is diminished. To sustain these through gene editing, exact gene editing methods and strict regulation of metabolic processes are used to produce sustained and effective production without compromising cell viability. Concerns of societal acceptability and regulation also surround gene food modification, particularly with relation to genetically modified organisms (GMOs). It is a challenging procedure to stabilize expression and introduce omega-3 production pathways into cell cultures without interfering with metabolic abnormalities [30].

The effective absorption and storage of omega-3 fatty acids in the cultured tissue presents yet another significant obstacle. Because omega-3 lipids are highly unsaturated and oxidatively unstable, their stability and shelf life in the finished meat product are reduced. Furthermore, adding omega-3 sources to the culture media, like algal oils, can be expensive and may not always result in good cell uptake. Enhancing the omega-3 content and optimizing the fatty acid content to match that of real meat also entails optimizing the media and co-culture system (fat and muscle cells) and scaling these up for industrial application at competitive prices without sacrificing safety and nutritional value. [14].

5. Future challenges

There are various obstacles that long-chain omega-3 fatty acids, such as EPA and DHA, must overcome while producing cultured meat. Since these fatty acids include many double bonds, they are susceptible to oxidation, which reduces their stability and the product's shelf life. Currently, the main source, fish oil is expensive and unsustainable, and substitutes made from microalgae and genetically engineered organisms have their own problems with scale and cost [51]. The efficient absorption and integration of these hydrophobic omega-3s into cultivated cells is a major technical challenge. Using liposomes or other techniques to promote solubility in water-based culture media can be more complex and costly. Targeted distribution that mimics the fatty acid profile of conventional meat is very challenging to achieve. To get the right meat texture and nutritional composition, omega-3s must be carefully balanced because they may also disrupt cell differentiation [52]. Lastly, the sector needs to manage governmental approval and consumer acceptability, particularly for innovative chemicals and genetically modified sources.

Conclusion

The pursuit of fortifying cultured meat with omega-3 fatty acids represents a significant step toward developing a more nutritionally robust and sustainable food source. This exciting concept, however, is far from a simple reality. The successful incorporation of these essential fatty acids is a complex undertaking that requires sophisticated technological solutions. Researchers are currently tackling intricate challenges, including optimizing the metabolic pathways within cultured cells to efficiently absorb and retain omega-3s, preventing lipid oxidation during the cultivation process, and developing scalable bioreactor systems that can precisely control the necessary environmental conditions. The journey from laboratory-scale experiments to widespread commercial production of omega-3-enriched cultured meat is a testament to the fact that this field is still in its nascent stages, demanding continuous innovation and significant technological advancements to overcome its inherent scientific and engineering hurdles.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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