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Can cell-cultured meat from stem cells pave the way for sustainable alternative protein?

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ABSTRACT

As the global population grows, the demand for food and animal-derived products rises significantly, posing a notable challenge to the progress of society in general. Alternative protein production may adequately address such a challenge, and cell-based meat production emerges as a promising solution. This review investigates methodologies for *in vitro* myogenesis and adipogenesis from stem cells (adult, embryonic, or induced pluripotent stem cells - iPSCs) across different animal species, as well as the remaining challenges for scalability, the possibility of genetic modification, along with safety concerns regarding the commercialization of cell-cultured meat. Regarding such complexities, interdisciplinary approaches will be vital for assessing the potential of cell-cultured meat as a sustainable protein source, mimicking the sensory and nutritional attributes of conventional livestock meat whilst meeting the demands of a growing global population while mitigating environmental impacts.

1. Introduction

Cell-cultured meat production aims to create an alternative to traditional meat using cell and tissue culture methods. Cells, sourced from animals, undergo *in vitro* cultivation and differentiation into muscle or fat cells. Through tissue engineering techniques, these cells can be organized into structures that mimic the sensory attributes of conventional meat (Schaefer and Savulescu, 2014; Treich, 2021). Cellular agriculture is an innovative sector that uses biotechnology to replace or minimize animal-derived products. Hence, adopting cell-cultured meat holds promise for generating meat items with reduced environmental impact and improved animal welfare standards.

Traditional livestock farming has been shown to impose significant and concerning stress on the environment due to the extensive consumption of resources to produce meat products (Campbell et al., 2017; Scollan et al., 2010; Petrovic et al., 2015), with relevance to climate change (Bellarby et al., 2013). The global population is projected to increase; consequently, global meat consumption is expected to increase (Gerber et al., 2013). The cell-cultivated meat offers a promising solution to the environmental, animal welfare, and public health challenges associated with traditional livestock farming. Utilizing cells to grow muscle and fat tissue diminishes the necessity for raising livestock, thus putatively mitigating greenhouse gas emissions (Jones, 2023), minimizing the loss of natural habitats and the resulting decline in global biodiversity (Hannah Ritchie et al., 2022), as well as decreasing water consumption and land use.

Biomanufacturing cell-cultured meat begins with selecting one or more starting cell populations. These cells must be capable of self-renewal and differentiation within a controlled environment into skeletal muscle cells and adipocytes. Multipotent or progenitor cells are commonly chosen due to their ability to differentiate into the required cell types (Arnhold and Wenisch, 2015; Dumont et al., 2015; Stout et al.,

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2022). For instance, satellite cells, the adult skeletal muscle stem cells, are relatively accessible and require minimal input to differentiate into skeletal muscle cells. Myoblasts, the progeny of satellite cells, are used to create cell-cultured meat prototypes. However, isolating and culturing these cells result in limited cell yield, necessitating multiple tissue collections for industrial-scale manufacturing.

Pluripotent stem cells, such as embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs), have overcome such difficulties by enabling the production of large numbers of myogenic progenitors without the need for repeated tissue sampling (Chal et al., 2016; Chal and Pourquié, 2017; Świerczek et al., 2015). Notably, the plasticity of iPSCs can contribute to both basic and applied fields due to their potential for recapitulating *in vitro* myogenesis, as demonstrated in human models for biomedical purposes (Chal et al., 2015, 2016; Chal and Pourquié, 2017).

Among the challenges related to cell types, two other significant obstacles to cell-cultured meat production are the media with non-animal-derived substrates and the development of large-scale bioreactors at affordable costs (Zhang et al., 2022; Sugii et al., 2023). For instance, the first cultivated beef burger was consumed globally in 2013, costing $325,000 (Jones, 2023). However, new cellular expansion alternatives have been studied to reduce the price and the use of animal-derived supplements, such as fetal bovine serum (Messmer et al., 2022; Ng et al., 2020; Stout et al., 2022). Additionally, emerging alternatives include hydrolysates derived from rice, yeast, or soy, which offer a diverse source of nutrients for animal cells (Ho et al., 2021). Algae have also been explored as a source of glucose and amino acids during the culture of mouse myoblast strains (Okamoto et al., 2020; Park et al., 2021).

For further cell culture, constructing an efficient extracellular matrix (ECM), scaffold, or degradable support materials where target cells can grow remains a significant challenge (Xu et al., 2023a, 2023b). Using structures made from bioproducts often avoids functional cell-to-cell junctions due to abnormal cellular textures. During expansion in 2D or 3D, the cells may alter their behavior depending on the microenvironment (Abbasnezhad et al., 2023). Nonetheless, support structures are essential for guiding cell growth and tissue shape (Rao et al., 2023).

Developing products with nutritional, structural, and sensory attributes similar to conventional meat promotes the advancement of biofabrication processes, enabling the transition from laboratory-scale to commercial-scale manufacturing (Chen et al., 2022; Dolgin, 2020; Ye et al., 2022). Nevertheless, technological and sometimes biological assets still hampered the large-scale production and commercialization of cell-cultured products. For example, using animal-free reagents while reducing costs to guarantee broad product access is a significant and well-discussed limitation nowadays. Furthermore, the quality and reproducibility of the final product are still under debate. Hence, new technologies that enable easy scalability and are unique during the first steps of the process may ensure rapid progress and robustness to the desired final product.

1.1. *Multipotent and progenitor cells*

Satellite cells (SCs) are considered myogenic stem cells or progenitor cells capable of self-renewal, muscle regeneration, and hypertrophy (Stout et al., 2022; Jeong et al., 2014). SCs are found between the sarcolemma and the basal lamina of skeletal muscle fibers; they are activated by muscle damage when regulatory myogenic factors (MRFs) released in the environment stimulate their proliferation, differentiation, and fusion of new multinucleated muscle cells. SCs isolation and *in vitro* maintenance have been well established (Li et al., 2015; Ding et al., 2018), and they do not differentiate into other cells except muscle fibers (Ding et al., 2021; Reiss et al., 2021) (Fig. 1). Due to such properties, they have recently become the most used in producing cell-cultured meat. On the other hand, the senescence in long-term culture is a limitation in large-scale cell-cultured meat production (Skrivergaard et al., 2023; Furuhashi et al., 2021). A continuous supply of SCs on a large scale would be necessary to address this issue. These cells are obtained through a tissue biopsy or post-mortem tissues from the species and the desired site of interest, commonly known as primary cells.

Due to the large number of cell types in muscle, such as endothelial cells, epithelial cells, and blood cells, among others, for a homogenous population of SCs, precise isolation is necessary (Guan et al., 2022). For that, two methodologies can be used: fluorescence-activated cell sorting (FACS) and magnetic-activated cell sorting (MACS) (Choi et al., 2020). For quality SCs, the ideal type of donor animal is essential; factors such as size (Daughtry et al., 2017), age (Neal et al., 2012), muscle type (Zhu et al., 2013), breed, and sex are important parameters in the growth and differentiation of isolated SCs (Daughtry et al., 2017). The standard markers for SCs are PAX7 (Seale et al., 2000), Syndecan-4 (SDC4,

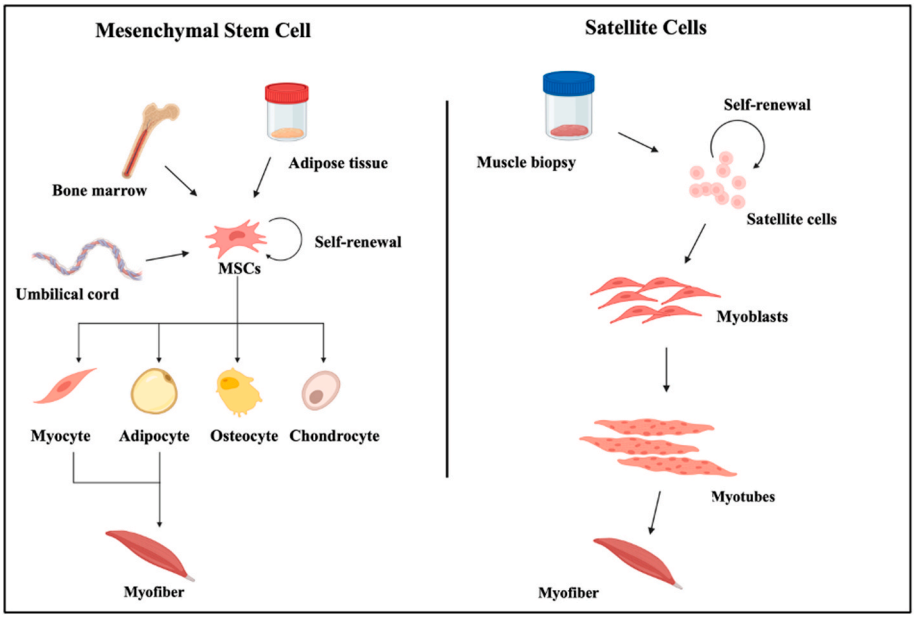

Fig. 1. Potential use of mesenchymal stem cells (MSCs) or satellite cells for cell-cultured meat production. The left panel shows MSCs derived from multiple sources, differentiating into myocytes, adipocytes, chondrocytes, and osteocytes. The right panel shows satellite cells differentiating into muscle fibers.

Cornelison et al., 2001; Tanaka et al., 2009), CXC chemokine receptor type 4 (CXCR4), and alpha-7 integrin, VCAM-1, CD56, M-cadherin (Bornemann and Schmalbruch, 1994). When satellite cells differentiate into myoblasts, they express the transcription factor MyoD (Tapscott et al., 1988). On the other hand, fibro/adipogenic progenitors (FAPs) play an important role in the myogenic organization (Musina et al., 2006; Biferali et al., 2019) due to form the connective and fatty tissues of meat; they can be found in the interstitium of skeletal muscle (Uezumi et al., 2010; Uezumi et al., 2011). The combination of FAPs and satellite cells can lead to forming of all cell types present in bovine meat; however, despite their ability to differentiate into mature meat cells, these adult stem cells have a limited expansion capacity, losing potency after a few passages in culture (Redondo et al., 2017).

Mesenchymal stem cells (MSCs), as an essential role in cell-cultured meat due to their multipotent plasticity, can differentiate into adipocytes, chondrocytes, myocytes, and osteoblasts (Piñeiro-Ramil et al., 2019) and it could substitute the FAPs during the cell-cultured meat. MSCs can be isolated from adipose tissue (Aust et al., 2004), muscle tissue (Jackson et al., 2010), umbilical cord (Corrao S. et al., 2013), and bone marrow (Shi and Gronthos, 2003), and present the surface markers CD90, CD105, and CD73 (Nombela-Arrieta et al., 2011).

A muscle biopsy is sufficient to obtain a cell population of MSCs, which are isolated and expanded to ensure an adequate number of cells for cell-cultured meat production. For the specific isolation of each cell type, unique markers expressed by the respective cell types are used. To acquire enough cells to sustain a culture and a posterior differentiation process, the cells need to be expanded after isolation, for which an ideal culture medium is necessary to provide the nutrients required for cell development. Generally, the culture medium is consistent with the species and types of cells being used.

Traditional 2D culture has been the primary cultivation method for years; however, it cannot replicate the conventional meat environment. In consequence, to allow the production in a higher magnitude, new methods and techniques such as bioreactors (Das et al., 2019; Jossen et al., 2018; Lawson et al., 2017), multicellular organoids/spheroids (Cesarz and Tamama, 2016; Yin et al., 2016), and chip systems (Wu et al., 2020) have been created and improved, allowing for 3D culture with a heterogenous cell culture, representing then a similar environment to the *in vivo* myogenesis (Nikolits et al., 2021; Chaicharoenaudomrung et al., 2019). Hence, 3D culture requires more cells, is more complex, and is labor-intensive, making 2D culture the most suitable for initial cultivation until now.

1.2. Pluripotent stem cells

PSCs, such as ESCs or iPSCs, have the plasticity to differentiate into the three germ layers: mesoderm, endoderm, or ectoderm. Due to this ability, the cells emerge as an option to develop cell-cultured meat, as they can be differentiated into all the cell types needed to produce cell-cultured meat (Chal and Pourquié, 2017; Świerczek et al., 2015) (Fig. 2). Moreover, these cells can be cultured long-term without losing their pluripotency, overcoming the challenges of working with multipotent or progenitor cells. ESCs, Epiblast Stem Cells (EpiSCs) or iPSCs have been used for myogenesis *in vitro* development in different species such as swine (Zhu et al., 2023a, 2023b) and humans (Bruge et al., 2022; Chal et al., 2015, 2016; D. Guo et al., 2022; Vu Hong et al., 2023), for translational regenerative medicine or animal production via cell-based meat development. However, isolating ESCs or EpiSCs from embryos is unfeasible, resulting in ethical and religious barriers.

In 2006, Takahashi and Yamanaka (2006) induced murine fibroblasts into a pluripotent state using overexpression of OCT4, SOX2, NANOG, and c-MYC. These cells had similar morphological and molecular characteristics as ESCs. With the development of iPSCs, the barriers to working with ESCs have been overcome, making the development of autologous therapies possible. The acquisition of iPSCs has been reported in different species such as humans (Y. Guo et al., 2018; Qi et al., 2018; Souza et al., 2021; Takahashi et al., 2007; T. Zhou et al., 2011), bovine (Bessi et al., 2021; Botigelli et al., 2022; Han et al., 2011; Su et al., 2021; L. Zhao et al., 2017), swine (Fujishiro et al., 2013; Li et al., 2018a; Machado et al., 2021; Pieri et al., 2021; Recchia et al., 2022; West et al., 2010), and others (Yoshimatsu et al., 2021a).

The integrative approach is the most efficient and commonly used methodology to reprogram somatic cells into a pluripotent state. For example, the use of lentivirus as a carrier to introduce the transcription factors into the cell has been reported as efficient (Bressan et al., 2020; Sommer et al., 2009); however, it generates transgenic iPSCs and could imply difficulties in differentiating the cells due to the non-silencing of the exogenous factors or the possibility of reactivation of those factors after differentiation. New methodologies focusing on non-integration have been approached, such as chemical (Fu et al., 2018; Y. Zhao et al., 2015) or episomal reprogramming (Li et al., 2018b; Okita et al., 2011; Tang et al., 2019; Yoshimatsu et al., 2021b; Yoshimatsu et al., 2021; Y. ye Zhou and Zeng, 2013; Zhu et al., 2023a, b); however, they remain less efficient than integrated methodologies and have not been elucidated for all species.

The generation of mature muscle cells *in vitro* from hiPSCs has been

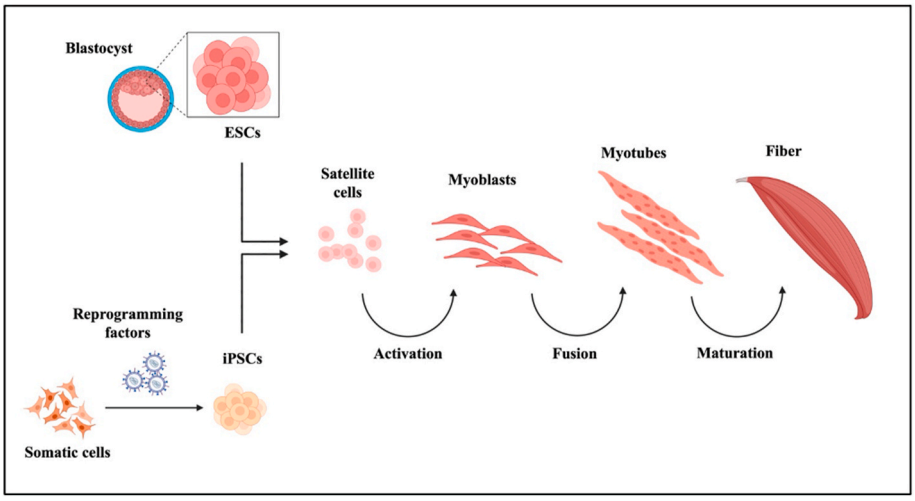

Fig. 2. Pluripotent stem cell differentiation for cell-cultured meat production. Embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) can both differentiate into satellite cells (SCs). The SCs undergo activation, generating myoblasts that start the fusion process, forming myotubes, which mature into muscle fibers.

achieved within one month. A heterogeneous cellular culture, including myoblasts and SCs (Chal et al., 2015, 2016), is observed during the process. Notably, the application of this biotechnology in animal models can lead to the development of new techniques for *in vitro* animal protein production. Recently, Zhu and collaborators (2023) optimized Chal's (2016) protocol for swine, leading to the differentiation of swine EpiSCs into myoblasts, further cultivated in a 3D scaffold resulting in a three-dimensional meat-like tissue. Nonetheless, the successful differentiation of the initial cell into desired mature cell types with a high yield is crucial for cell-cultured meat production. With iPSCs, this differentiation can be achieved, paving the way for large-scale production. This aspect makes iPSCs particularly promising for cell-based meat production.

1.3. Envisioning the transformative potential of induced pluripotent stem cells for creating sustainable, cell-cultured meat

Since induced pluripotent cells can be differentiated into several cell types, they can form cells and tissues that make up fresh meat, allowing its production *in vitro*. Thus, the use of iPSC cells for industrial meat production can be considered an ecologically clean alternative, in contrast to extensive livestock farming, since iPSC culture does not require the use of large areas, such as pastures, nor does it lead to large-scale waste production, such as pig farming. In *vitro* meat production by differentiating iPSC cells may reach a highly scalable process. Since there is no need to maintain large herds, an *in vitro* meat production plant could add elements of verticality to its structure. In other words, unlike pastures that require a large horizontal land extension, an iPSC meat factory could be housed in a multi-story building, for example, providing a viable real estate alternative for large urban centers.

Another advantage brought by iPSC-derived food is the possibility to create healthier meats when compared to their natural counterparts since the final product has the potential to contain nutrients in a previously modeled quantity, such as, for example, a desired proportion of saturated and polyunsaturated fats, or even the replacement of nutrients with lower nutritional value by other healthier nutrients (Bhat et al., 2015). Theoretically, meat production through differentiation of iPSC cells could also reduce the speed of meat production. The ideal time for slaughtering cattle is around two years and can reach up to four years, depending on the cattle confinement model, while for pigs, the slaughter age varies from 130 to 170 days, to which 114 days of gestation are added (Bortoluzzo et al., 2011; EMBRAPA, 2013; EMBRAPA, 1998). *In vitro* meat, on the other hand, has a production time of between three and four weeks (Ding et al., 2021), which ensures greater speed for production, as well as a reduction in the resources used; however, of course, scalability is still needed to achieve such achievement.

Finally, further possible advantages of *in vitro* meat production are the possibility of producing meat from exotic animals and the appeal from the market regarding socio-cultural movements against the slaughter process inherent to the livestock production method (Bhat et al., 2015) due to the possibility of generating the iPSCs-derived meat using noninvasive methods.

Several factors still hamper the performance and large-scale use of iPSCs for food production. Amongst the most important, the defined animal-free, including serum-free conditions of cell culture, are already well discussed (Quek et al., 2024), which directly implies the scalability of the process and, certainly, the success of efficiently differentiating stem cells into the functional tissues that comprise the muscle that will turn into meat. Importantly, for livestock pluripotent stem cells, the lack of well-defined protocols for differentiation is the critical step to be surpassed (Martins et al., 2024). Hence, we will present recent data on farm species' *in vitro* myogenesis protocols, aiming to provide solid information for future development and reproducibility.

1.4. Myogenesis in farm species

1.4.1. Fish

Since aquaculture and fishing generate a large amount of waste (e.g., fins), new technological alternatives can utilize the waste to produce *in vitro* meat through cell differentiation using fin-derived primary cultures, obtaining stable fibroblast-like cells for further differentiation into different cell lineages composing the meat fillet (Tsuruwaka and Shimada, 2022). However, recreating a structure similar to fish fillets in the laboratory is still challenging (Xu et al., 2023a, 2023b). Cell culture information is scarcer than mammals (Saad et al., 2023). Recent studies demonstrate that fish fillet-like tissues were obtained after the proliferation and differentiation of SCs in 3D scaffolds constructed from gelatin-based gels and formed a muscular structure filled with *in vitro* cultured adipocytes (Xu et al., 2023a, 2023b). However, the methodology requires different inhibitors to prevent fibrosis and increase myogenic efficiency, such as LY411575 (a Notch inhibitor) and RepSox (a TGFβR-1/ALK5 inhibitor).

Fish cells offer advantages for *in vitro* meat production compared to other species, such as chickens and pigs (Potter et al., 2020). For example, fish cells have shown a greater capacity for duplication before senescence (Graf et al., 2013), a more stable karyotype (Barman et al., 2014; Fan et al., 2017), and can be cultured in atmospheric air (Potter et al., 2020; Tsuruwaka and Shimada, 2022). Interestingly, fish stem cell culture can be performed to force cell differentiation into specific lineages by expressing transcription factors as in mammals (Hong et al., 2011), suggesting that the genetic mechanisms by which cells can be reprogrammed are conserved across species (Rosselló et al., 2013). However, determining the ideal culture conditions for fish cells that promote the differentiation of fibroblast-like cells into various cellular morphologies is still necessary (Tsuruwaka and Shimada, 2022). Thus, determining the optimal conditions for cell culture and differentiation will depend on the biological characteristics according to the species, including incubation temperature (cold water or warm water species) and the compositions of maintenance and growth media (freshwater or marine species) (Salmerón, 2018).

On the other hand, whilst induction media have the same compositions as in mammals, some differences have been described. During the differentiation of fibroblasts into iPSC, some authors have used egg or embryo extract for iPSC induction due to genetic factors obtained from maternal inheritance, growth factors activated during embryonic development, or unidentified factors released by oocyte and embryonic microenvironments that could promote cell reprogramming (Meilany et al., 2017; Peng et al., 2019; Badyaev A.V. Maternal Inheritance, 2013; Lubzens et al., 2017; Tadros and Lipshitz, 2009; Proietti et al., 2019), while other authors have succeeded in inducing fibroblast differentiation without using fish blood or embryo extracts (Rosselló et al., 2013; Tsuruwaka and Shimada, 2022). Table 1 presents further differentiation attempts regarding fish cell lines.

1.4.2. Swine

Monogastric animal meat production (pigs and poultry) in 2022 accounted for 73 percent of the global output. From this share, pork meat production (122.59 million tons) contributed for 47 percent, consolidating it as the second largest source of animal protein globally (Ritchie, 2024;Ritchie and Roser, 2024). Despite its prominence in global protein production, pig farming is associated with environmental impacts such as greenhouse gas emissions, nitrogen emissions, and pollution of rivers and water sources. According to Dalgaard et al. (2007), analyzing the Danish pork meat production line, each kilogram of pork meat generated 3.2 kg of CO_2 emissions. Nitrogen emissions from livestock supply chains represent about one-third of the permissible ceiling for sustainable planetary limits in CO_2 emissions, with the pig production chain accounting for 16 percent of these emissions (Uwizeye et al., 2020).

In addition to environmental impacts, factors such as herd health

Table 1
In vitro myogenesis protocols in different species: fish, porcine and bovine.

Author(s)	Cell type	Methodology	Target	Characterization
Fish				
Benjaminson et al. (2002)	Muscle fiber cells and satellite cells, epithelial cells, blood cells, nervous tissue, and connective tissue.	Differentiation: MEM in Hanks' salts, 10% FBS at 23 °C. CCM (crude cell mixture) serving as a substrate.	Resembled fish fillets	Tissue explant measurements
Saad et al. (2023)	Satellite cells of Atlantic mackerel (*Scomber scombrus*)	**Expansion:** Leibovitz's L-15 Medium, with 20% fetal bovine serum, 1 ng/mL hFGF with antibiotics and antimycotic **For lipid accumulation:** Growth medium with 10 μg/ml insulin, 0.5 mM 3-isobutyl-1-methylxanthine, 0.25 μM dexamethasone, and 10 μL/ml lipid mixture at 27 °C without CO2	Muscle fiber and adipogenic-like cells	PCR, RT-qPCR immunocytochemistry, Lipidomics
Xu et al. (2023a), b	Preadipocytes of Large yellow croaker (*Larimichthys crocea)*	**Isolation and expansion:** DMEM with 15% fetal bovine serum (FBS), 15 mM HEPES, and antibiotics. **Differentiation:** Isolation medium with hormones: 10 μg/mL insulin, 0.5 mM 3-isobutyl- 1-methylxanthine (IBMX), 0.25 mM dexamethasone, and 10 μg/mL lipid mixture, which contained 4.5 g/L cholesterol, 10 g/L cod liver oil fatty acids, 25 g/L polyoxyethylene sorbitan monooleate, and 2.0 g/L D-α-tocopherol acetate.	Adipocytes	Histology, ultrastructural observation, RT-qPCR, lipid staining
Gabillard et al. (2010)	Satellite cells rainbow trout (*Oncorhynchus mykiss*)	**Expansion:** F10 + 10%FCS **Differentiation:** DMEM+2%FCS in laminin-coated tissue culture plates Culture at 18 °C.	myogenic cells	Immunofluorescence, western blot analysis
Myhre and Pilgrim (2010)	Embryonic stem cells of zebrafish (*Danio rerio*)	Expansion and differentiation: 25% DMEM, 25% L-15, 50% Hank's saline Serum,10% FBS, 5% carp serum, CaCl, L-Gln, 10% Zebrafish embryo extract HEPES/saline buffer and insulin in laminin-coated culture plates.	Myocyte	RT-qPCR, ICC, and histology
Xu et al. (2023a), b	Piscine satellite cells (PSCs) of Large yellow croaker (*Larimichthys crocea)*	**Maintenance:** high-glucose DMEM containing 15% FBS and 1% P/S cultured at 27 °C. **Myogenic differentiation:** F12 medium containing 8% HS, 10 ng/ml IGF- 1, 50 nM necrosulfonamide, 200 μM ascorbic acid, 1% P/S, **Adipogenic differentiation**: DMEM/F12 medium containing 10% HS, 10 μg/ml insulin, 0.5 μM IBMX, 0.25 μM dexametha- sone, 1% Lipid Mixture, 1% P/S. **3D culture:** differentiation medium supplemented with fish gelatin, pig gelatin, silk fibroin, hyaluronic acid, and chitosan. Sodium alginate was used to prepare a hydrogel precursor solution. Cell viability in 3D culture improved: 200 μMPifithrin- α hydrobromide and 0.1 μM XMU-MP-1a were used.	Tissue-like Fish fillets Muscle tissue formation under the guidance of a biomimetic model of scaffold	RNA-seq, transcriptomic analysis immunofluorescent, histological staining, rheology measurement, textural analysis, and tissue clice staining
Tsuruwaka and Shimada (2022)	Fibroblast-like cells of Thread-sail filefish (*Stephanolepis cirrhifer)*	**Expansion:** L-15 media containing 10% FBS and 1% Zell Shield in Collagen I Coated flask at 25 °C. **Differentiation:** AIM V Medium +10% FBS and L-15 + 10% heat-inactivated SeaGrow	Skeletal muscle-like cells and adipocyte	Lipid stainig, inmmunofluorescence, and morphology
Porcine				
Genovese et al. (2017)	Naïve piPSC modified to impart ectopic MYOD1 activity	A hybrid approach, using piPSC modified to confer ectopic MYOD1 activity, with simultaneous exposure to 5AC and CHIR99021	Skeletal myotubes	Immunodetection, flow cytometry, and Ca^{2+} transient analyses.
Yu et al. (2022)	piPSC	Differentiation medium followed by seeding in 3D gelatin scaffolds	Endothelial cells	Sorting through flow cytometry.
Liao et al. (2018)	piPSC	Adipogenesis medium	Osteoblast-like	Alizarin Red Staining, ICC.
Aravalli et al.	piPSC	Derived from embryoid bodies with RPMI medium containing B27 and activin A	Hepatocyte-like	RT-qPCR, ICC, periodic acid Schiff assay.
Ding et al. (2017)	Pig muscle tissue	fluorescence-activated cell sorting	Highly purified porcine satellite cells	Immunofluorescent analysis, RT-qPCR.
Choi et al. (2020)	Pig muscle stem cells	**Isolation and maintenance:** SkGM-2 supplemented with 20 μM SB203580. **Differentiation:** MEM,2% horse serum, glutamax, non-essential amino acids, 0.1 mM β-mercaptoethanol.	Expansion of pig Muscle stem cells Myofiber	RT-qPCR ICC.
Zhu et al., 2022	Porcine muscle stem cells	**Differentiation:** Matrigel and DMEM supplemented with 2% horse serum **Maintenance:** 100 μM l-Ascorbic acid 2-phosphate added to the culture medium.	Myotubes similar to muscle fibers;	ICC, Western blots, RT-qPCR, proteomic analysis.

(*continued on next page*)

Table 1 (*continued*)

Author(s)	Cell type	Methodology	Target	Characterization
Zhu et al. (2023a), b	Pig epiblast stem cells	Serum-free medium for cell differentiation	3-D meat-like tissue	Karyotype analysis, flow cytometry, ICC, RT-qPCR, transcriptome and sequencing
Li et al. (2021)	Porcine muscle satellite cells	3D bioprinting	Porcine skeletal muscle tissue	immunofluorescent staining and cell viability assessment
Bovine				
Will et al. (2015)	Satellite cells	**Isolation and expansion:** DMEM F12, glutamine 0.02 M, 1% P/S, 10% de FBS. **Differentiation:** DMEM/F12 0.5 mg/mL BSA, 0.1 nM dexamethasone, 100 μg/ml transferrin, 0.5 μg/ml linoleic acid, 1 μM insulin, 1 μM cytosine arabinoside	myotube	ICC: Desmin.
Furuhashi et al., 2021	Myocyte	**Myocyte maintenance and expansion:** DMEM, 10% SFB, 50 μg/ml gentamicin sulfate, 10% SFB. **Differentiation:** DMEM 2% Horse Serum (HS), 50 μg/mL gentamicin sulfate, 100 μM de ascorbate phosphate e 100 ng/ml IGF-1.	Muscle fiber-like (3D)	ICC: α-actinin
Yu et al. (2023)	Satellite cells	**Isolation and maintenance:** DMEM 10/20% FBS, 1%P/S. **First differentiation (3D)**: DMEM 2% HS, 1%P/S. **Second differentiation** (4D): DMEM 10% HS, 1%P/S.	Myotube	MitoTracker® ICC: MYOD and MF20
Skrivergaard et al., 2021	Satellite cells	**SCs maintenance and expansion:** DMEM 0.2 mg/mL gentamicin, 200 U/mL penicilin, 0.2 mg/mL, 5 μg/mL amphotericin B. **Differentiation:** DMEM F12, 10% de FBS, 10% de HS, 1 mM sodium pyruvate, and 1% P/S + amphotericin B. **For differentiation and maintenance** plus 5% FBS.	Myotube	RT-qPCR: *MYF5; MYOD1; MYF6; MYOG; PAX7* and *MEF2A*. ICC: MYOSIN
Bhat et al. (2015)	Primary myoblasts	**Isolation and maintenance:** Advanced DMEM, 20% FBS, 10% HS, 4 mM L-Glutamine and 1% Penicilin/Streptomycin/Amphotericin-B. **Serum-free media:** Several basal commercial medias were tested: FGM-CD SingleQuots Kit™, StemPro™ MSC SFM, Essential 8™ Medium, STEMmacs™ HSC Expansion Media XF, mTeSR1™, MesenCult™ ACF Culture Kit and TeSR™-E8™. All supplemented with 5% LipoGro™ and 6% XerumFree™.	Myoblasts	Cell viability measurement
Yu et al., 2023	Satellite cells	**Isolation and maintenance:** Han's F10 Nutrient Mix, 20% FBS and 1% P/S. **Serum-free media maintenance:** six serum-free commercial media were tested: Han's F10 Nutrient Mix, NutriStem hPSC XF medium, CellGenix® GMP Stem Cell Growth Medium, Essential 8™ Medium, StemFlex™ Medium, Cellartis® MSC Xeno-Free Culture Medium 1 Kit and Mesenchymal Stem Cell Growth Medium DXF. **Differentiation:** Han's F10 Nutrient Mix, 2% FBS and 1% P/S.	Satellite cells and Myoblasts	Cell viability measurement, RT-qPCR: *PAX7, MyoD*, and *MyoG*. ICC: PAX7, MyoG and MyoD.
Defendi-Cho and Gould., 2023	Embryonic tracheal fibroblast cell line	**Maintenance media:** DMEM, 10% FBS and 1% P/S. **Serum-free maintenance media:** DMEM, 10 g/L CVE (*Chlorella vulgaris* extract), 10% CGF (chlorella ghowth factor) and 1% P/S.	Embryonic tracheal fibroblasts cell line	Cells viability measurement (MTS) and imaging

also affect global pork meat production. Diseases of high pathogenicity, such as African swine fever, which is highly transmissible among domestic pigs and wild boars, can have a significant negative impact on global pork meat production (Sánchez-Cordón et al., 2018; Woonwong et al., 2020). As an alternative to conventional pork meat production, cell-cultured meat is associated with a response to standard meat production's ethical and environmental paradigms (BRYANT, 2020). Commercial production of cell-cultured porcine meat still faces technological impediments, such as the need for standardized efficient bioreactors and support from upstream and downstream industries for mass production of supplies such as culture medium (Humbird, 2021; CHEN et al., 2022).

Current techniques for cell-cultured meat production consist of obtaining and expanding stem cells, differentiation into myoblasts, induction to fusion to form myotubes and, subsequently, muscle fibers, and developing the system (Kadim et al., 2015). Some specific protocols have already been reported for the expansion of porcine muscle stem cells. For example, Choi et al. (2020) suggest the use of minimum essential medium (MEM) supplemented with 10% fetal bovine serum, glutamine, non-essential amino acids, and 0.1 mM β-mercaptoethanol) or Skeletal Muscle Cell Growth Medium-2 BulletKit™ (SKGM-2; Lonza, Basel, supplemented with 20 μM SB203580); and MEM supplemented with 2% horse serum, glutamine, non-essential amino acids, and 0.1 mM β-mercaptoethanol have been reported for myogenesis.

ZHU et al. (2022) report parameters for cell-cultured porcine meat production: a minimum of 107 stem cells were necessary to produce 1 kg of cell-cultured porcine meat, a considerably smaller number of cells than the 1011 mentioned by Bellani et al. (2020). It was also pointed out

the need to accelerate the expansion stage by adding 100 μM l-Ascorbic acid 2-phosphate to the culture medium to prevent markers of muscle cells PAX7 and MyHC from reducing their expression during culture.

Cell-cultured meat production requires the continuous maintenance of a flow of new stem cells, so it does not eliminate the need for animal slaughter. An alternative to circumvent this limitation may be induced pluripotent porcine stem cells (piPSC). Since these induced pluripotent cells can proliferate indefinitely (YAMANAKA, 2020), their use in substitution for muscle stem cells in the cell-cultured meat production process may allow for the complete elimination of the need for animal slaughter.

The generation of non-integrative and transgene-free piPSCs still represents a challenge. Li et al. (2018) presented a model for generating intermediate porcine-induced pluripotent cells, non-integrative and transgene-free, capable of expressing Yamanaka factors (Oct4, Sox2, c-Myc, and Klf4), differentiating into the three germ layers, and forming embryoid bodies, indicating that these cells can differentiate into muscle tissue and be used in cell-cultured porcine meat production. Conrad et al. (2024) reported the reprogramming of transgene-free piPSCs from porcine fibroblasts by reprogramming with episomal vectors and the use of a plasmid containing microRNA-302/367 cluster co-electroporated to increase reprogramming efficiency.

Regarding piPSC differentiation, Genovese et al. (2017) presented a model for differentiating piPSCs into skeletal myotubes using a hybrid approach. They used CHIR99021 to prevent cell death during differentiation, a modified piPSC lineage to confer ectopic MYOD1 activity, and exposure to 5-aza-cytidine (5Aza), which were reported as activators of pathways for myogenic differentiation in cell lineages.

1.4.3. Bovine

Much has been discussed about the water usage, carbon release, and putative high consumption of natural resources related to traditional meat production through beef cattle farming (Steinfeld et al., 2006). These justifications have been intensively used to justify the cattle *in vitro* meat, and indeed, in 2013, the first beef burger made from cultured cells was launched. Since then, various cultivation processes have been developed in order to improve and produce a quality, safe, and low-cost meat product.

During bovine embryonic development, the somite gives rise to skeletal muscles. Notch and Wnt signaling is responsible for the expression and inhibition of essential cells at this stage, Pax3 and Pax7 (Musumeci et al., 2015), which are myogenic progenitors that need factors such as MYF5, MRF4, and MYOD to differentiate into myoblasts (Zammit, 2017). For complete differentiation into myotubes, MYOG, MYOD, and MYHC need to be expressed (Rudnicki et al., 1993; Acevedo and Rivero, 2006).

Will and colleagues (2015) isolated and cultured bovine satellite cells for 5 days in a growth medium containing 10% SFB; after reaching confluence, culture media were tested with and without the addition of SFB, obtaining a fusion rate of 30% in the serum-free medium after 72 h of differentiation. Desmin labelling was performed by immunocytochemistry to determine the degree of muscle differentiation. Moreover, Furuhashi and collaborators (2021) implemented the 3D culture method containing bovine myocytes in a hydrogel, resulting in a muscle fiber-like tissue after 14 days of culture; they saw that the base for cultivation made of fibrin and Matrigel associated with electrical stimulation had a rate of 50 % of myotubes containing α-actinin.

Yun et al. in 2023, adapted the protocol for porcine satellite cell isolation and differentiation to (Lee et al., 2021) bovine. It started with muscle cell tissue collection, where the satellite cells were isolated and expanded with F10 medium supplemented with bFGF and later differentiated and maintained with DMEM culture medium and 10% FBS. After detecting positive markers such as MyoD and Mf20, they have shown a more effective differentiation procedure with lower costs, resulting in myotube cell type (Yun et al., 2023).

Skrivergaard et al. (2021) analyzed the proliferation and myogenic differentiation capacity of bovine satellite cells concerning the time the sample was taken, taken at 2 h post-mortem, 2–5 days, and after 5 days stored at 40C, verifying that the period of sample collection above 5 days of storage shows a low level of viability, using myotube markers such as Myosin MHC previously characterized by Zammit (2017) and myogenic markers MYF5, MYOD1, MYF6 and MYOG as well as PAX7 and MEF2A RT-qPCR, however the samples taken within 2 h and those from 2 to 5 days had no negative impact on their myogenic power.

To produce cultured meat similar to conventional meat, muscle fibers, and other types necessary for tissue connection, such as chondrocytes, circulatory cells, and adipocytes, are needed (Post et al., 2020). Multipotent or progenitor cells can differentiate these cell types depending on their capability of self-renewal and their potency to differentiate them (Arshad et al., 2017).

It is essential to mimic the *in vivo* environment during the *in vitro* myogenesis to produce cultured meat similar to conventional meat; muscle fibers, the culture media, and supplementation are some of the significant challenges to modulating the correct pathways to induce the differentiation, as well the matrix used to grow. However, most supplements are animal-derived, which implies the sustainability expected from the cultivated meat; moreover, a culture of cells without animal-derived supplementation remains challenging to differentiate and maintain the cell in culture efficiently. In 2020, Kuo and collaborators presented the formulation of a medium called B8, suitable for cultivating and maintaining hiPSCs, which costs an average of 3% of commercial media, which was optimized by Stout et al., (2022). It has been shown to support the maintenance and expansion of bovine cells, making it an exciting option for serum-free media (Stout et al., 2022).

1.5. Micronutrients, macronutrients and ageing of cultured meat

At present, the study of the nutritional composition of *in vitro* meat remains notably incomplete. Lee et al. (2024) reported that protein and lipid production in cultivated meat is associated with the stiffness of the scaffold, with more rigid scaffolds favoring protein production and less rigid scaffolds favoring lipid production. Lie et al. (2022) and Pasitka et al. (2023) have shown that cultivated meat appears to have protein, lipid, and mineral levels comparable to traditional meat. However, studies analyzing micronutrient concentrations, such as vitamins, are still lacking.

O'Neill et al. (2021) highlights that cell culture could require specific media formulations, given the variety of cells being simultaneously cultured—such as myotubes, satellite cells, and myoblasts. Considering these variations, the composition of amino acids in the culture medium can lead to differences in the sensory profile of the final product. Thus, the culture medium must also be optimized considering the sensory profile generated in cultivated meat.

According to Purslow (2024), the literature on post-harvest metabolic processes in cultivated meat is insufficient, lacking detailed studies describing the mechanisms involved in cell death. These processes can lead to significant alterations in the sensory and textural profiles of cultivated meat. Purslow, for example, has noted that the lack of connective tissue may lead to unfamiliar sensory characteristics compared to traditional meat.

It is essential to discuss that traditional "*in vivo*"-derived meat presents several molecules and biomarkers known to control the quality and composition of the final product, as already reviewed (Berri et al., 2019). However, such information is scarce in "lab-grown" meat. As most of these markers may be related to the genetics of the animals, using stem cells already known for their genetic background, such as the iPSCs, may favor the quality or at least the characteristics expected for each final product, when derived from known cell lineages.

1.6. Limitations of technology

Introducing innovative "clean meat" products remains a significant

challenge compared to animal-derived products. Major challenges include high costs, scalability, biological problems, and all other questions derived from these, such as nutritional value, aging, and sustainability. New strategies need to be adopted to promote new alternatives, and some specific challenges are yet to be deciphered, including the similarity of flavors, texture, nutritional and microbiological quality, and scalability. The maturation and ageing of the muscular tissue are complex (Purslow et al., 2016), and they could not be reproduced *in vitro*.

One important aspect, however complex, is the production of cultured meat with different fat percentages, considering that muscle and fat adhere differently to growth substrates (Potter et al., 2020), and due to the reduction in the duplication and differentiation performance of muscle cells by adipose tissue secretions (Pellegrinelli et al., 2015). For example, studies have been conducted using noncommercial fish species (zebrafish and medaka) because these meats present low-fat content compared to other aquatic products such as salmon (Cai et al., 2024; Potter et al., 2020).

Implementing an efficient extracellular matrix (ECM), scaffold, or degradable support materials in which target cells can grow remains challenging (Xu et al., 2023a, 2023b) for cell-based meat production without animal-derived products. The use of structures made from bioproducts often avoids functional cell-to-cell junctions due to abnormal cellular textures (Abbasnezhad et al., 2023).

Notably, the final product is yet to be improved to any comparison to be made. Although biologically similar tissues are now possible to be constructed in a very similar 3D environment, the nutritional, technological, and sensorial attributes are yet to be deciphered and routinely employed for the safe consumption of these new products (Broucke et al., 2023; Fraeye et al., 2020). Mostly due to such challenges, the industry is investing significantly less in the development of cell-cultured meat in the last years, possibly due to the leading to significant scientific advancements and overcoming obstacles.

One limitation of recent stem cell-derived cultured meat is the use of progenitor cells derived from biopsies, which provides a limited proliferative capacity and rate of the initial cell population. In this context, induced pluripotency, as stated previously in this discussion, may pave the way for obtaining scalable, differentiated cell types *in vitro*.

1.7. Future perspectives

Alternative proteins of various types are emerging in the market, such as plant-based meat, edible insects, and cell-cultured meat, all aiming to meet the demand for meat. However, these alternative protein sources also face constant challenges; for example, plant-based meat products often fall short in terms of the sensory quality of traditional meat (Lee et al., 2020); and similarly, promising protein sources such as edible insects require greater consumer acceptance for widespread consumption (Wilkinson et al., 2018).

In this context, cell-cultured meat is one of the most promising alternative protein sources, produced through *in vitro* culture, proliferation, and differentiation of animal-derived cells (Alexander et al., 2017). It has gained prominence for the last years; however, the number or food companies or startups investing or receiving investments has not been exponentially rising as it was some years ago (State of the Industry Report, Cultivated meat and seafood, GFI., 2023; Hocquette et al., 2024).

Cell-cultured meat production also has the potential to offer new job opportunities for highly skilled individuals (Coucke et al., 2023; Morais-da-Silva et al., 2022) due to the technical issues involved. The effectiveness of marketing interventions to promote the new method of meat production to consumers is necessary due to perceptions of unnaturalness and feelings of repulsion among the population (Septianto et al., 2023). Terms such as “clean meat” or “lab-grown meat” are acceptable to consumers (Krings et al., 2022; Thorrez and Vandenburgh, 2019). However, for a large portion of the population, the new alternative food production method is challenging to understand, so terms such as “cellular” have been more favorable for promoting safe products (Malerich and Bryant, 2022). However, further research is needed to compare consumer preferences among different types of meat analogs (Coucke et al., 2023).

From an academic standpoint, this scientific field is still very new, and the knowledge required for the biotechnology and techniques necessary to start a production system is scarce. The collaboration between industry and academia is needed and has been implemented by startups and multinational corporations. To develop an efficient process, many areas within research need to be aligned, including the isolation and characterization of stem cells, optimization of growth media, design of bioreactors and cell culture expansion, three-dimensional structures, and sensory and nutritional evaluations. The subject is still very controversial and requires much more investment from basic and applied sciences (Hocquette et al., 2024). In this context, induced pluripotent stem cells are a perspective to be further explored and may contribute to solving some of the most critical limitations reported until now.

2. Conclusion

In conclusion, cell-cultured meat emerges with the promise to be part of the solution to the growing demand for sustainable and cruelty-free food. At the same time, technological and biological pitfalls still may hamper its large-scale production and consumption. Although traditional meat replacement may not be the central aim, new technologies are emerging and may help surpass most conventional meat production disadvantages, creating an alternative product. This review has joined various protocols for developing myogenesis *in vitro*, using different types of cells, highlighting the potential and the barriers needed to overcome, including scaling up production to meet global demands and ensuring the safety of these products.

In particular, we highlight the possibility of overcoming some of the most critical challenges of culture meat production on a large scale through induced pluripotency. Such technology aims to provide an unlimited variety of cell lineages derived from noninvasive cell isolation from live individuals, which contributes not only to the meat production itself but also may provide an ideal platform for meat modeling and analysis before consumption approval by ethical and legal authorities. iPSCs have already proven their feasibility and use in treating several conditions in regenerative medicine, and herein, we discuss their potential for sustainable food generation.

An interdisciplinary approach and collaborative effort between academia and industry are crucial to making cell-cultured meat a reality on dinner plates. It is essential to discuss the real necessity of ensuring that cell-cultured meat can mimic conventional meat’s taste, or whether an alternative product with similar nutritional value, economically viable, may be accepted by consumers. Overall, more investments and research can overcome the challenges of industrial production and achieve the desired sensory characteristics.

Author contribution

All authors have made substantial contributions to all of the following.

1. The conception and design of the study.
2. Drafting the article or revising it critically for important intellectual content.
3. Final approval of the version submitted.

Declaration of competing 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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Data availability

Data will be made available on request.

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