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Cellular agriculture — industrial biotechnology for food and materials

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Fundamental changes of agriculture and food production are inevitable. Providing food for an increasing population will be a great challenge that coincides with the pressure to reduce negative environmental impacts of conventional agriculture. Biotechnological manufacturing of acellular products for food and materials has already been piloted but the full profit of cellular agriculture is just beginning to emerge. Cultured meat is a promising technology for animal-based proteins but still needs further development. The concept of plant cells as food offers a very attractive alternative to obtain healthy, protein-rich and nutritionally balanced food raw material. Moreover, cultured microbes can be processed into a wide range of biosynthetic materials. A better control over structural properties will be increasingly important in all cultured cell applications.

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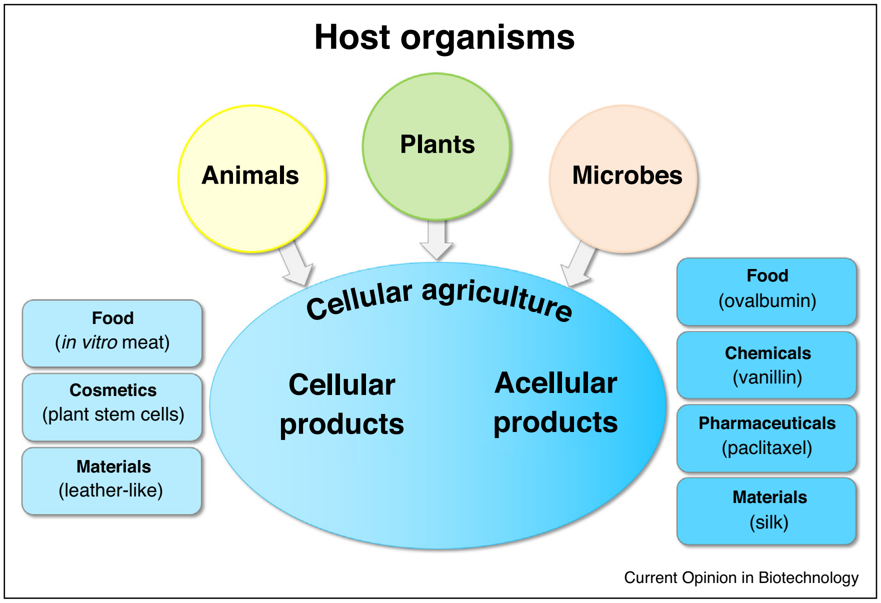
Introduction

Transforming the current food system simultaneously towards the goals of providing healthy diets and environmental sustainability constitutes one of the grand challenges of current times. Achieving these targets is a fundamental prerequisite to meet the UN Sustainable development Goals (SDGs) (https://www.un.org/sustainabledevelopment/sustainable-development-goals/). Even though global food production of calories so far kept pace with population growth, there is on the one hand still a significant gap in providing sufficient food and on the other hand, there are concurrent problems with low-quality diets causing micronutrient deficiencies and diet-related obesity [1••]. It appears unlikely that conventional agriculture alone can cope with the huge challenges ahead. Current estimates project 60% higher global food requirements by 2050 [2] while only 2% more agricultural land is available ultimately covering 40% of total land area. Contrary to common belief, human activity, including domestication of livestock, adaptation of agriculture and the industrial revolution causing a dramatic increase in the human population, has actually decreased total biomass on Earth by a factor of two rather than increasing it [3]. This is mainly due to forest management and grazing [4]. Crops account only for ca. 2% of all plant biomass on the globe [4]. This figure includes non-food crops, too, and shows that the conflict of growing either food or biomass for materials such as fibre — and more recently for fuel — is serious [5]. In conclusion, it is apparent that efficient alternatives for food and material production are desperately needed.

Industrial biotechnology holds the key to provide humanity with nutritious, safe and healthy food together with chemicals and innovative materials while minimizing resource input such as energy, land and water in addition to gaining seasonal and geographical independence and reducing waste. Biotechnology in the form of several waves, that is, the red, green and white biotechnology has already made a huge impact on the modern society and economy [6]. Green biotechnology enabled the green revolution, that is, a massive yield increase of crops through breeding varieties with, for example, improved agronomic traits, nutritive value and disease resistance [7]. The principal focus of the red and white biotechnology has been on acellular products, that is, compounds with pharmaceutical applications, fine and bulk chemicals with a wide spectrum of uses such as food additives and supplements, pigments, flavours, aroma components, polymer building blocks and fuels. More recently, there has been an increased interest in cellular products to be used as food, cosmetics and materials. The term 'cellular agriculture' [8] has been proposed, that is, utilization of cell cultures of the whole variety of host organisms (Figure 1) for the production of agricultural commodities rather than production by farmed animals or crops.

In this review article, we focus on the cellular products that are at this point exclusively non-GM. We refer the reader to literature outlining production of acellular products mostly in genetically modified microorganisms. An

Figure 1



Schematic representation of cellular agriculture. Host organisms are covering animal, plant and microbial cells. Cellular products with examples are shown on the left and acellular products with examples on the right.

example for a food ingredient is ovalbumin [9], for chemicals vanillin [10] and for materials silk proteins [11].

Animal cells

Meat is an important dietary source of many components supporting growth and development of the human body and maintaining health over the lifetime. However, the consumption of especially red meat has lately been associated with a high risk of cardiovascular diseases, type 2 diabetes and certain cancers, that is, colon cancer due to saturated fatty acids and carcinogenic compounds formed in food processing of red meat. Negative impact caused by meat-related foodborne illnesses, for example, avian flu or swine fever as well as ethical issues have also gained a lot of attention [12].

Animal agriculture is one of the major contributors to several environmental problems being responsible for about 10% of greenhouse gas emissions in U.S. alone, and globally for about 37% of all methane emission [13]. The consequences include climate change, water and air pollution as well as deforestation. At the same time, the growing population, increased welfare in the developing countries and changed dietary practices have led to a tremendous rise in demand of food proteins, especially animal-derived proteins, and hence increased meat consumption. Moreover, especially the cattle meat production is inefficient as the conversion rate from feed to animal protein is low, approx. 15% [14]. Because of the enormous ecological footprint of livestock, particularly cattle, on the landscape globally, the food disruption, especially cellular agriculture offers great opportunities for keeping the environment healthy.

Artificial meat refers to meat substitutes that can be divided basically into three categories: meat alternatives from plants and fungi, meat from GM animals, and cell-based meat. We deal in this review only with cell-based meat, also called clean meat, lab-grown meat or *in vitro* meat. It is a complex food product comprised of animal cells - mainly skeletal muscles, fat and connective tissues such as myoplasts or other microcarriers [15]. The myosatellite or adipose stem cells are grown in growth medium outside an animal in a bioreactor. They are multipotent cells, capable of transdifferentiation, and therefore need to be reharvested from time to time [16]. Cell-based meat is genetically identical to conventional animal meat but hard to develop due to structural complexity. Moreover, the texture that contributes strongly along the taste is hard to mimic. In fact, ground meat is far simpler to replicate than steaks, and competitive alternatives will enter the market all the time. The 3D printing might be an option to mimic a steak from cultured meat [17]. Already now a big trend, although not new, is to replace animal proteins with biotech-derived ingredients such as tofu, seitan or tempeh, and more recently fungal protein product Quorn. However, cell-based meat may still have an advantage in the long run from a consumer perspective as it is animal meat. On the other hand, this is not an option for vegetarians and vegans.

The first slaughter-free hamburger based on laboratory-cultured meat was unveiled in 2013 by the CSO of Mosa Meat, Professor Mark Post. The cost at that time was estimated 250 000 € [14]. Since then a lot of interest has been raised to replace the production of animal agriculture meat by cellular agriculture. This is not an easy task as the cultured meat needs to have preferably the same nutritional value as animal-produced beef with similar taste, flavour, texture and appearance. However, when the technology advances the costs also fall. The major problems still are the need to use animals for obtaining appropriate cells and expensive, animal-derived serum as a basic component of the growth medium for cell proliferation and differentiation, as well as the scalability of the process [18•]. The latter is a challenge due to the growth pattern of the animal cells attached to surfaces. However, alternative production systems such as producing only needed animal proteins by microbes, are necessary because at current prices, revenues of the U.S. beef and dairy products which today exceed about 400 billion dollars are estimated to decline by 50% by 2030 [19••]. In addition, other livestock and fisheries will follow the same trend. Therefore, the major producers of animal products are globally at serious economic risk.

Plant cells

The environmental impact (per kg of product) of crop farming for human consumption is much lower than that of animal products but in total still accounts for at least one third of all agricultural impact due to the high production volumes and larger food loss and waste [20]. Reducing the environmental footprint is therefore one important driver to consider industrial biotechnology of plant cells for food applications. Although life cycle analyses to determine concrete savings in water consumption and so on. are largely missing, initial studies, concentrating on process optimisation [21], indicate a significant potential in cost and resource reduction. The wide adoption of 'plant stem cells', that is, dedifferentiated plant cells as a source for cosmetic ingredients [22] is strongly driven by consumer demand for sustainably sourced ingredients, too [23]. Cell culture technology was a prerequisite to access and exploit rare plants while securing supply without further endangering wild populations. Most cosmetic products in this segment are derived from cell culture extracts but a number of formulations contain whole cells [24•] and therefore fall into the cellular agriculture category covered by this review.

Another impulse for the utilization of plant cells as food originates from nutritional recommendations to increase dietary intake of plant-based food altogether [1••]. There is already a strong trend towards substitution of animal proteins with plant-based alternatives such as soy and pulses. However, many crops contain small amounts of certain essential amino acids compared to most animal-derived proteins [25]. In general, the digestibility of crop proteins in their natural form is lower than the proteins from animal sources [26], which can be due to anti-nutritional factors [27], interaction and/or physical entrapment with compounds. Interestingly, recent investigations concerning the nutritional composition of cultured plant cells revealed very favourable contents of approximately 21–37% dietary fibre, 0.3–1.3% starch, 18–33% sugars as well as good quality lipids besides 14–19% protein [28••]. The samples showed balanced profiles of nutritionally essential amino acids exceeding contents of soy protein isolates and most importantly exhibited differential digestibility, a basis for efficient absorption, depending on species and processing [28••].

In contrast to animal cell cultures, there is a long history of plant cell cultures for the production of secondary metabolites including food ingredients at scale. Based on the pioneering work of Haberland describing cellular totipotency [29], rapid technological development took place to firmly establish methods for heterotrophic cell culture in bioreactors. First commercial products, mainly secondary metabolites as pharmaceuticals, appeared on the market in the 1980s [30]. An impressive case illustrating how technically advanced plant cell culture is, provides the production of the anti-cancer drug paclitaxel in 75 000 liter bioreactors to meet most of the global demand [31]. It is somehow surprising that the explicit use of entire plant cells as food has only recently been suggested [32] despite the established practice to exploit tissue and organ cultures of ginseng for food supplement production in Asia [33].

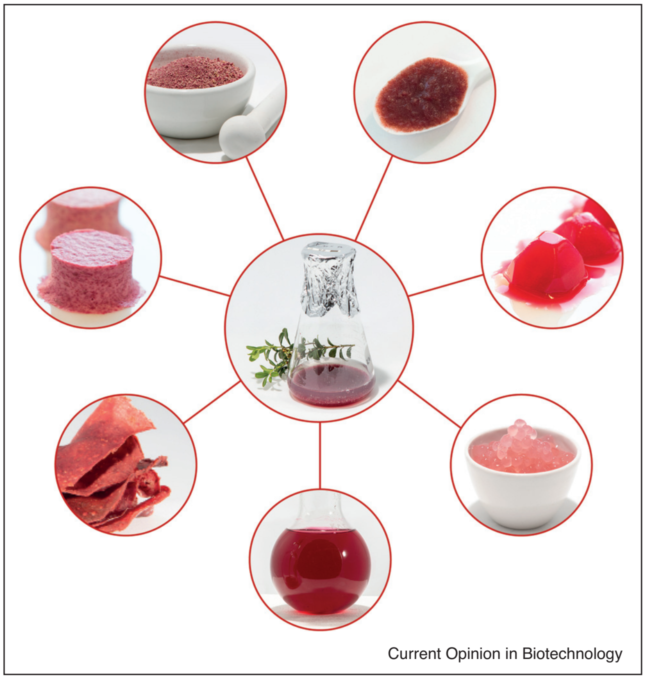
Plant cell culture medium is chemically fully defined and consists mostly of inorganic ingredients, that is, salts, sugar (usually sucrose) as carbon source and some low concentration vitamins and phytohormones. It is therefore much less complex and costly as compared with animal cell culture medium. Since many cosmetics are already economically produced from plant cells [24•] it is realistic that at least luxury food such as, for example, chocolate made from plant cells [34] will soon follow once suitable processing methods for the biomass have been established. As proof of concept, we have processed cell cultures derived from lingonberry in different ways to showcase the broad versatility of the raw material (Figure 2).

Plant cells could serve as material constituents, too, although even less work has been published in this area. Since plant cells do not adhere to surfaces in cultures but rather grow as single cells or cell aggregates, tissue-like 3-dimensional structuring of the cells is a major obstacle. 3D printing approaches could lead the way towards achieving ordered growth [35].

Microbial cells

Whole-cell microbial production of food protein has long been established and commercialised. Since this so called 'single cell or myco-protein' must always undergo processing due to nutritionally unfavourable high contents of

Figure 2



Cultured plant cells as versatile raw material for various future food applications. Center: Lingonberry plant cell culture. Clockwise from top right to bottom: Acellular products — filtered cells, gelled 'cubes', agarose encapsulated pearls, cell extract. Counter-clockwise from top left to bottom left: Cellular products — lyophilized powder, structured 'patties', structured and dried 'crisps' (Photos by Heiko Rischer).

RNA and since the topic has been rigorously reviewed before [36] this aspect of cellular agriculture is not covered here.

Microbes can also be cultivated to make synthetic materials. In nature, macroscopic materials grown from microbes, such as biofilms, mushrooms, and lichens, have little relevance as synthetic structural materials. However, microbes can be used to produce various polymers and polymer precursors for materials [37,38]. An emerging field aims to use the microbial growth process as such for producing synthetic materials [39]. The challenge is to control the growth and morphogenesis of the cells to make tissue-like materials. This material fabrication using living organisms is often termed as material biofabrication [40] and is related to biofabrication for tissue engineering and regenerative medicine.

An interesting material example is fungal mycelium which can be grown into sheets or composite materials [41]. Filamentous fungi grow as long hyphae by tip extension and branching, and eventually form a fibrillar network [42]. Interestingly, for centuries, humans have used fruiting bodies of bracket fungi to make leather-like textile materials [43]. Today, designers [44•] and researchers (Figure 3) are reviving this almost forgotten art and are able to control the mycelium growth into desired materials and shapes. In fact, the company Ecovative Design has pioneered the use of mycelium as a material component [45]. Fungal mycelium can be grown into bio-based solid composites, foams, and leather-like non-woven fabrics [41]. Importantly, many filamentous fungi secrete a range of hydrolytic enzymes for the breakdown of lignocellulosics and other organic substrates and therefore are able to convert waste streams into materials.

Figure 3

Headset 'Korvaa' demonstrating the use of microbially produced materials (URL: https://www.fastcompany.com/90354704). The design demo is made from bioplastics, leather-like mycelium materials, synthetic spider silk, protein-cellulose foam, and a composite of mycelium and bacterial cellulose. The headset was designed by Aivan (www.aivan.fi), and the materials were produced by VTT Technical Research Centre of Finland Ltd and Aalto University (Photo by Thomas Tallqvist, courtesy of Aivan).

The fungal cell wall forms a well-connected network and essentially bears the structural role in the material [46•]. However, the understanding of molecular and genetic factors affecting hyphae biomechanics is currently limited. It has been shown that cell wall chitin content affects material tensile properties [47] and that cell wall proteins have a role in mycelium density and consequently in material strength [48].

Other microbes have also been shown to form materials. Alkalitolerant bacterial cells, such as some *Bacillus* species, can be cultured to form biomineralized bricks in a microbially induced calcite precipitation process [49]. Microbial cells and virus particles can also be grown for biotemplating the synthesis of nanoparticles [50]. *Gluconacetobacter* can be cultivated to produce very pure cellulose non-woven films and recently also 3D shapes [51]. Interestingly, bacterial cellulose films have been shown to be able to entrap microalgae into a moldable hydrogel, demonstrating a synthetic symbiosis between the two species [52].

It is important to note that the described bottom-up material fabrication processes are guided by the genetic information of the growing cells. Thus, understanding the relevant genetic factors will be highly important for the design of novel biosynthetic functional materials. Advances on this front have already been demonstrated such as the growing of adaptive pollutant binding materials [53], paving the way for engineered living materials [54••].

Conclusions

Biotechnological production of acellular compounds has already and is still affecting many industries because it facilitates substitution of conventional processes with sustainable and economic alternatives. Cellular products are just beginning to emerge and bear potential to disrupt food, cosmetics and material production. However, as these products are more visible for the end-users it is of outmost importance to ensure consumer acceptance. In the case of food products, processing to beneficially modulate flavour and texture needs to be developed. Safety must be ensured by following respective regulatory frameworks for food [55] and cosmetics [56]. Once all these conditions are met, sustainability is proven, and economic cases drawn up, then the technology could face a real breakthrough.

Authors'contributions

All authors (Heiko Rischer, Geza Szilvay, Kirsi-Marja Oksman-Caldentey) contributed equally to:

Writing — Original Draft: Preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation), finalizing the submitted manuscript.

Heiko Rischer and Kirsi-Marja Oksman-Caldentey contributed equally to:

Writing — Review & Editing: Preparing the revised version of the manuscript; responding to reviewers' comments.

Conflict of interest statement

Nothing declared.

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