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MINI-REVIEW

Towards *chlorocytes* for therapeutic intravascular photosynthesis

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Abstract

Aerobic metabolism relies on external oxygen production through photosynthesis and its subsequent transport into each cell of the body via the cardiorespiratory system. This mechanism has successfully evolved over millions of years, enabling animals to inhabit most environments on Earth. However, the insufficient oxygen supply leads to several clinical problems, ranging from non-healing wounds to tumor resistance to therapy. Given that photosynthetic microorganisms are capable of producing oxygen and removing carbon dioxide from the environment, over the last decade, several groups worldwide have proposed their potential use as an alternative tissue oxygenation approach. While most studies have demonstrated safety and efficacy after local tissue administration, recent studies have also suggested that systemic administration could trigger intravascular photosynthesis. If successful, the development of a new generation of circulating cells, known as *chlorocytes*, may partially replace the role of erythrocytes in gas exchange within the body, without relying on external supply and vascular flow. This work reviews the existing literature on local and systemic administration of photosynthetic microorganisms, highlighting the main challenges in the field and potential solutions to unleash the enormous potential clinical impact of *chlorocytes* and intravascular photosynthesis.

Key points

- *Circulating photosynthetic microorganisms could deliver oxygen to tissues*
- *Microalgae and cyanobacteria have shown safety and efficacy for oxygen delivery*
- *Several key challenges need to be addressed for the clinical success of chlorocytes*

Keywords Hypoxia · Oxygen delivery · Photosynthesis · Microorganisms · *Chlorocytes* · Cyanobacteria · Microalgae

Introduction

Molecular oxygen is an essential molecule for life, required for various fundamental processes. Among its crucial roles, oxygen acts as the final acceptor for electrons in mitochondria during oxidative phosphorylation, contributing to the synthesis of adenosine triphosphate (ATP) and, subsequently, energy production (Murphy, 2009). Moreover, oxygen plays a pivotal role in the immune response by facilitating the oxidative killing of bacteria by producing and releasing reactive oxygen species (ROS) by macrophages and neutrophils (Slauch 2011; Nguyen, Green & Mecsas, 2017). Additionally, ROS are essential for cell signal transduction, activating several signaling pathways, transcription factors, and others (Averill-Bates, 2024). Consequently, animals require a continuous external supply of oxygen to live.

Given the substantial dependence of animals (including humans) on an external oxygen supply, insufficient tissue oxygenation represents a key pathophysiological factor in numerous acute and chronic conditions, affecting millions of patients worldwide each year. Conditions such as cardiovascular diseases (Abe et al. 2017), hemorrhages (White et al. 2017), anemia (Varlotto & Stevenson 2005), asphyxia (Solevåg et al. 2019), and ischemia–reperfusion injuries (Tasoulis & Douzinas 2016) are particularly relevant among acute cases. On the chronic side, clinical problems like tumor resistance to various treatments (Muz et al. 2015; Jing et al. 2019), abnormal tissue fibrosis (Darby & Hewitson 2016), and the development of non-healing chronic wounds (Tandara & Mustoe 2004; Desmet et al. 2018) are also linked to prolonged exposure to insufficient oxygen supply.

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The cellular and molecular mechanisms behind insufficient oxygen supply may vary among different conditions; however, they all share the common aspect that the organism cannot deliver the right amount of molecular oxygen produced during photosynthesis to tissues. Given this impairment, over the last decade, several research groups worldwide have proposed that photosynthetic microorganisms could be used as direct local oxygen delivery systems to hypoxic tissues (Dawiec-Liśniewska et al. 2022; de Andrade et al.. 2022), including skin wounds (Obaid et al. 2021), myocardial infarction (Cohen et al. 2017), and tumors (Ma et al. 2024). Moreover, in recent years, the use of such photosynthetic cells for intravascular tissue oxygenation has also been explored, representing a potentially groundbreaking emerging technology still in its early stages. This approach is based on the idea that these photosynthetically active "green cells," or *chlorocytes*, may partially replace the physiological function of erythrocytes; however, several crucial technological challenges must be addressed interdisciplinarily before its clinical implementation.

Therefore, this review will provide an overview of photosynthesis and tissue oxygenation, briefly summarizing the works that have already explored the potential use of photosynthetic microorganisms for local tissue oxygenation and intravascular photosynthesis. This will be followed by a discussion highlighting the main challenges in the field and some of its potential solutions. Finally, we will discuss the expected clinical impact of developing *chlorocytes* for vascular photosynthesis.

Photosynthesis and tissue oxygenation

In the eighteenth century, Antoine Lavoisier and Jan Ingenhousz made distinct but interconnected contributions to the current understanding of the chemical and physiological processes of gasses and respiration. Lavoisier is credited with identifying and naming oxygen and conducting meticulous experiments to prove its role in combustion and respiration, demonstrating that substances gain mass by combining with oxygen during these processes (Le Grand, 1972; Hendry 2005; West 2013). On the other hand, Ingenhousz's efforts laid the groundwork for understanding the physiological importance of oxygen, suggesting that plants release oxygen during the day and absorb carbon dioxide at night through photosynthesis, while animals consume oxygen and release carbon dioxide through respiration (Gest 1997; Magiels 2007; Hill 2012).

This last proposition implies a reciprocal relationship between plants and animals and represents the basis for the fundamental energy transfer from the sun and between organisms. Although Lavoisier and Ingenhousz ignored the cellular and molecular mechanisms of such reactions, it is now clear that photosynthetic organisms utilize the energy of light to break down the water molecule, releasing oxygen into the atmosphere as a metabolic byproduct.

During evolution, oxygen-based metabolism emerged as the dominant mechanism to obtain energy from reduced compounds, representing a critical challenge for multicellular organisms in ensuring sufficient oxygen supply to meet the respiratory needs of every cell (Lenton 2003). While diffusion-mediated oxygen transfer is efficient over short distances, larger organisms have to evolve sophisticated convective mechanisms for oxygen delivery, such as ventilation and circulation (Stamati et al. 2011). Apart from insects and some other small-sized *Arthropoda*, which use a trabeculae network to allow oxygen-rich air within tissues (Westneat et al. 2003), most terrestrial and aquatic species rely on lungs or gills, respectively, to facilitate and optimize oxygen uptake, where specialized epithelium allows gas exchange in these organs (Carvalho 2011). For effective exchange, this process requires the maintenance of a suitable concentration gradient across surfaces and further metabolic byproducts, such as oxygen and carbon dioxide, which is facilitated by the circulatory system. This system accomplishes both oxygen uptake at the lungs or gills and oxygen delivery in the vicinity of each cell by flowing oxygenated blood through a network of branching tubes conducting towards thin-walled capillaries that comprise an extensive exchange surface for oxygen diffusion from blood to cells (Hall, 2010).

This intricate network of branching vessels, including capillaries, facilitates oxygen delivery to tissues and carbon dioxide removal, having anatomical flexibility tailored to meet varying metabolic demands (Pozrikidis & Davis 2013). Blood flow distribution across organs and tissues is highly regulated by systemic and regional signals that allow for independent adjustment of blood flow in each tissue according to its local metabolic demand, subordinated to whole-body homeostasis (Clifford 2011; Reglin & Pries 2014). Thus, to ensure effective oxygen delivery, arteriolar dilation enhances the microvascular flow and optimizes the oxygen exchange area (capillary recruitment) to meet tissue-specific demands, such as during exercise (Ascolese et al. 2019; Fry, Roy & Secomb, 2013).

Within this context, erythrocytes play a pivotal role in oxygen transport, with hemoglobin's affinity for oxygen being modulated by physiological factors, including pH, temperature, and carbon dioxide concentration, as described by the Bohr effect (Jensen 2004). Erythrocytes also transport a substantial part of metabolically produced carbon dioxide from tissues to the lungs. Here, as proposed by the Haldane's effect, hemoglobin's affinity for carbon dioxide lowers as oxygen tension rises, contributing to overall carbon dioxide uptake in tissues and release in the lungs (Siggaard-Andersen & Garby 1973; Malte & Lykkeboe 2018). The intricate interplay of these mechanisms underscores

the complexity of oxygen delivery, highlighting the frail dependence of multicellular aerobic organisms on such a process.

Given the existence of a vast number of microorganisms capable of releasing oxygen and fixing carbon dioxide (Santos Correa et al. 2023), it is reasonable to hypothesize that if these photosynthetic cells could play a similar role within the vascular system, they could potentially overtake the function of erythrocytes for gas exchange and delivery in tissues. If successful, these so-called *chlorocytes* (Ehrenfeld et al. 2023) may have enormous consequences for human physiology and medicine.

Photosynthetic microorganisms for local tissue oxygenation

Photosynthetic therapies propose the induction of a symbiotic relationship between animal and plant tissues for the treatment of various hypoxic clinical conditions (Yang et al. 2023; Liu et al. 2023). Because illumination and follow-up are more accessible than in other conditions, external wound healing has received significant attention, and it has been used for over a decade as a proof-of-concept clinical model. Different biomaterials and photosynthetic microorganisms that produce oxygen upon illumination have been used to improve this process. As several excellent reviews are already available (Chávez et al. 2020; Han et al. 2023a; Ma et al. 2024), a short description of the topic is presented here.

Photosynthetic biomaterials were first introduced to alleviate hypoxia for in vitro tissue engineering (Hopfner et al. 2014) and further validated for skin regeneration in vivo (Schenck et al. 2015). Since then, different photosynthetic biomaterials have been designed to promote wound healing, including surgical sutures (Centeno-Cerdas et al. 2018), topical hydrogels (Li et al. 2021; Zhu et al. 2022; Corrales-Orovio et al. 2023; Wu et al. 2024), microneedle patches (Zhao et al. 2023; Gao et al. 2024), in situ bio-printed scaffolds (Wang et al. 2022a), and sprays (Chen et al. 2024). In recent years, several independent research groups have shown promising results of those materials by promoting wound healing in vivo, including diabetic mice (Chen et al. 2020; Younis et al. 2022; Wu et al. 2023; Zhao et al. 2023; Kang et al. 2024), ischemic wounds (Zhu et al. 2022), and infected wounds (Li et al. 2021; Hu et al. 2022; Chen et al. 2023a; Gao et al. 2024). Moreover, although commercial products are not yet available on the market, an ongoing clinical trial has shown for the first time that photosynthetic microalgae can be safely implanted in humans to promote full skin regeneration in patients (Obaid et al. 2021; Obaid et al. 2022).

Tumor treatment has also benefited from photosynthetic therapies. Since 2019 (Lee et al. 2019; Zhou et al. 2019), a bloom of independent studies has shown promising results by combining the oxygenation capacity of different photosynthetic microorganisms with other tumor treatment methods, such as photodynamic therapy (Zhou et al. 2019; Huo et al. 2020; Sun et al. 2020; Zhang et al. 2021a, 2021b; He et al. 2021; Qi et al. 2021; Wang et al. 2021a, 2022b; Chang et al. 2022; Lu et al. 2022; Ou et al. 2022), radiotherapy (Chai et al. 2022; Jiang et al. 2022), chemodynamic therapy (Lee et al. 2019; An et al. 2024), and sonodynamic therapy (Lu et al. 2022). Although most of the studies have been performed in subdermal tumors, a recent work describes the feasibility of this approach in a bone cancer model (An et al. 2024). These results have been recently reviewed (Ma et al. 2021; Yang et al. 2023; Han et al. 2023b), highlighting not only the efficacy of photosynthetic microorganisms for tumor treatment but also that their local administration did not elicit an evident activation of the immune response, demonstrating biocompatibility in vivo.

In addition to skin wounds and tumors, the biomedical use of photosynthetic microorganisms has also been explored to provide oxygen in other clinical contexts. For instance, an early groundbreaking study proposed a photosynthetic artificial lung using *Chlorella pyrenoidosa* to remove carbon dioxide and produce oxygen in a simulated patient (Basu-Dutt et al. 1997). More recently, microalgae were used to support encapsulated pancreatic islets within bioartificial pancreas constructs (Bloch et al. 2006; Evron et al. 2014), resulting in significant enhancements in islet function under perfusion-deprived conditions, while another study demonstrated that intraperitoneal implantation of microalgae improved graft recovery in pancreas transplantation in mice (Yamaoka et al. 2012). In a different approach, cyanobacteria were directly injected into the tissue to provide oxygen in murine ischemic hearts (Cohen et al. 2017) and brains (Wang et al. 2021b). Recent works have shown similar strategies using hydrogels for the delivery of photosynthetic microorganisms to ischemic hearts (Liu et al. 2022; Stapleton, 2023) and in a rheumatoid arthritis murine model (Guo et al. 2021). Finally, in addition to providing oxygen, cyanobacteria have been used to reduce local glucose concentration for treating diabetic retinopathy (Zhou et al. 2023).

These findings collectively highlight the multifaceted attempts to utilize diverse photosynthetic microorganisms as effective therapeutic agents to provide oxygen in different clinical scenarios, emphasizing the importance of optimizing illumination parameters and exploring organismal biodiversity for enhanced treatment efficacy.

Chlorocytes for intravascular oxygen supply

The studies mentioned in the preceding section have demonstrated the feasibility and safety of implanting different species of photosynthetic microorganisms in various in vivo models to provide oxygen locally in a controlled manner for treating different hypoxic conditions. However, limited research has investigated the potential use of circulating photosynthetic microorganisms to produce oxygen within the vascular networks of hypoxic tissues. Therefore, in this section, the existing literature about *chlorocytes* is reviewed, highlighting the versatility of photosynthetic microorganisms to address diverse therapeutic challenges, which suggests their potential application in a wide range of medical contexts.

Recent studies provide promising in vitro and in vivo outcomes into the safety of intravascular photosynthesis. In vitro experiments revealed the compatibility between the microalgae *C. reinhardtii* and endothelial cells that maintain their main morphological and functional characteristics after co-culture (Ehrenfeld et al. 2023). Furthermore, independent studies conducted in fully immune-competent rodents demonstrated that cyanobacteria and microalgae could be injected intravenously without eliciting a significant immune response (Williams et al. 2020; Ehrenfeld et al. 2023). After systemic injection, *S. elongatus* did not trigger acute or adaptive immune responses in rats, with no adverse effects observed in liver function or signs of damage in major tissues. Additionally, this study showed that the viability of cyanobacteria was affected after 4 h in circulation, demonstrating that the organism is capable of clearing the microorganism without deleterious consequences for the host (Williams et al. 2020). Similarly, no signs of distress or immune response were observed upon systemic administration of *C. reinhardtii* in mice (Ehrenfeld et al. 2023).

Systemic delivery of photosynthetic microorganisms has also been explored in the field of cancer treatment, demonstrating safety and biocompatibility in mice. For instance, the injection of modified *S. elongatus* with photosensitizer-encapsulated nanoparticles attached revealed no changes in IL-6 serum levels, hepatic and kidney function, or damage to major organs (Liu et al. 2020). Similarly, intravenous administration of *S. elongatus* modified with photosensitizer and photothermal agents revealed no changes in blood tests and histological analysis of major organs (Yin et al. 2023). Moreover, a therapeutic approach based on *Spirulina platensis* loaded with doxorubicin determined that the urinary system cleared the photosynthetic microorganism within 48 h, and routine blood and biochemistry tests were unaffected for at least 30 days after systemic delivery. Additionally, major organs showed conserved tissue structures without any apparent inflammatory lesions or damage at 60 days (Zhong et al. 2020a).

In addition to safety assays, the feasibility of different microorganisms to circule within the blood vessels has been demonstrated for microalgae and cyanobacteria, laying the groundwork for potential therapeutic vascular applications. For instance, intravascular delivery of *S. platensis* loaded with doxorubicin showed uptake in major organs, such as the lung, kidney, liver, stomach, and intestine (Zhong et al. 2020a). Interestingly, microalgae *C. reinhardtii* exhibited similarities to erythrocytes in size and non-Newtonian fluid behavior, reaching the entire body after systemic delivery without evidence of extravasation, demonstrating that microalgae could distribute throughout most tissues and organs, including the microvasculature (Ehrenfeld et al. 2023). Furthermore, *C. reinhardtii* was able to sustain oxygen production in mammalian media conditions and flowed through the entire vascular network in an ex vivo perfused porcine kidney, making this microalgae suitable for organ preservation (Veloso-Giménez et al. 2021). Remarkably, systemic administration of *C. reinhardtii* and *Synechocystis* sp. into *Xenopus laevis* tadpoles revealed the distribution of both photosynthetic microorganisms throughout the central nervous system vasculature, where they generated oxygen upon illumination (Özugur et al. 2021).

The efficacy of systemic administration of photosynthetic microorganisms has been mainly described for cancer treatment. For instance, the intravenous injection of modified *S. elongatus* with attached photosensitizer-encapsulated nanoparticles, in combination with laser irradiation, could eradicate primary tumors and prevent tumor recurrence and metastasis (Liu et al. 2020). Similarly, systemic administration of *S. elongatus* modified with photosensitizer and photothermal agents significantly prolonged the lifespan of tumor-bearing mice. Specifically, mice treated with engineered cyanobacteria and laser therapy achieved a 75% survival rate at 42 days post-delivery, whereas all mice in the control groups died (Yi et al. 2023). Additionally, the intravascular delivery of microalgae and cyanobacteria into *Xenopus laevis* tadpoles showed their capability to rescue neuronal activity by photosynthetic oxygen production (Özugur et al. 2021).

Additionally, several studies have proposed innovative coating strategies to reduce systemic clearance and enhance the efficacy of photosynthetic microorganisms in therapeutic interventions. Here, membrane coating using mammal cell-derived membranes has shown promise in enhancing tumor inhibition and reducing tumor growth. Interestingly, two independent studies showed that the accumulation of membrane-coated *C. vulgaris* in tumor tissue was more efficient than that of native microalgae (Qiao et al. 2020; Gao et al. 2023a). In addition, biomineralization coating has also demonstrated effective tumor suppression and anti-metastatic

capabilities without causing organ damage (Zhong et al. 2021; Li et al. 2020). Furthermore, the development of theragnostic agents (to identify and treat cancerous tumors) using superparamagnetic nanoparticles to coat *S. platensis* highlights the potential of coated photosynthetic microorganisms for effective therapeutic interventions (Zhong et al. 2020b), underscoring the efficacy of coated microorganisms in targeted cancer therapy.

Challenges for *chlorocytes* and potential solutions

As expected for a new research field, several key issues must be addressed before unlocking the transformative potential of *chlorocytes* in medicine and physiology (Fig. 1). While promising results have been observed regarding viscosity, rheological behavior, *chlorocyte* permeation into and through capillaries, and short-term safe interaction with the endothelium (Veloso-Giménez et al. 2021; Ehrenfeld et al. 2023), numerous hemodynamic challenges persist for vascular photosynthesis. For instance, the mid and long-term effects of circulating *chlorocytes* on endothelial integrity and function remain undefined, particularly concerning the maintenance of barrier function and permeability in the microvascular network. Additionally, further research is needed to elucidate the impact of *chlorocyte*s on the release of endothelial-derived paracrine signals such as nitric oxide, prostacyclin, and endothelin in arterioles and conduit vessels, as well as their effect on adhesion molecules. In this regard, another critical topic is ensuring *chlorocyte*-free passage through the microvasculature, which is essential for maintaining blood flow and vascular resistance. While the small size of cyanobacteria would prevent capillary clogging, most microalgae are in a size range equaling or exceeding that of erythrocytes, potentially compromising passage through microvessels. Furthermore, the spherical shape and presence of a cell wall in microalgae do not facilitate deformation upon reaching the capillaries, unlike the highly deformable biconcave disc shape of erythrocytes.

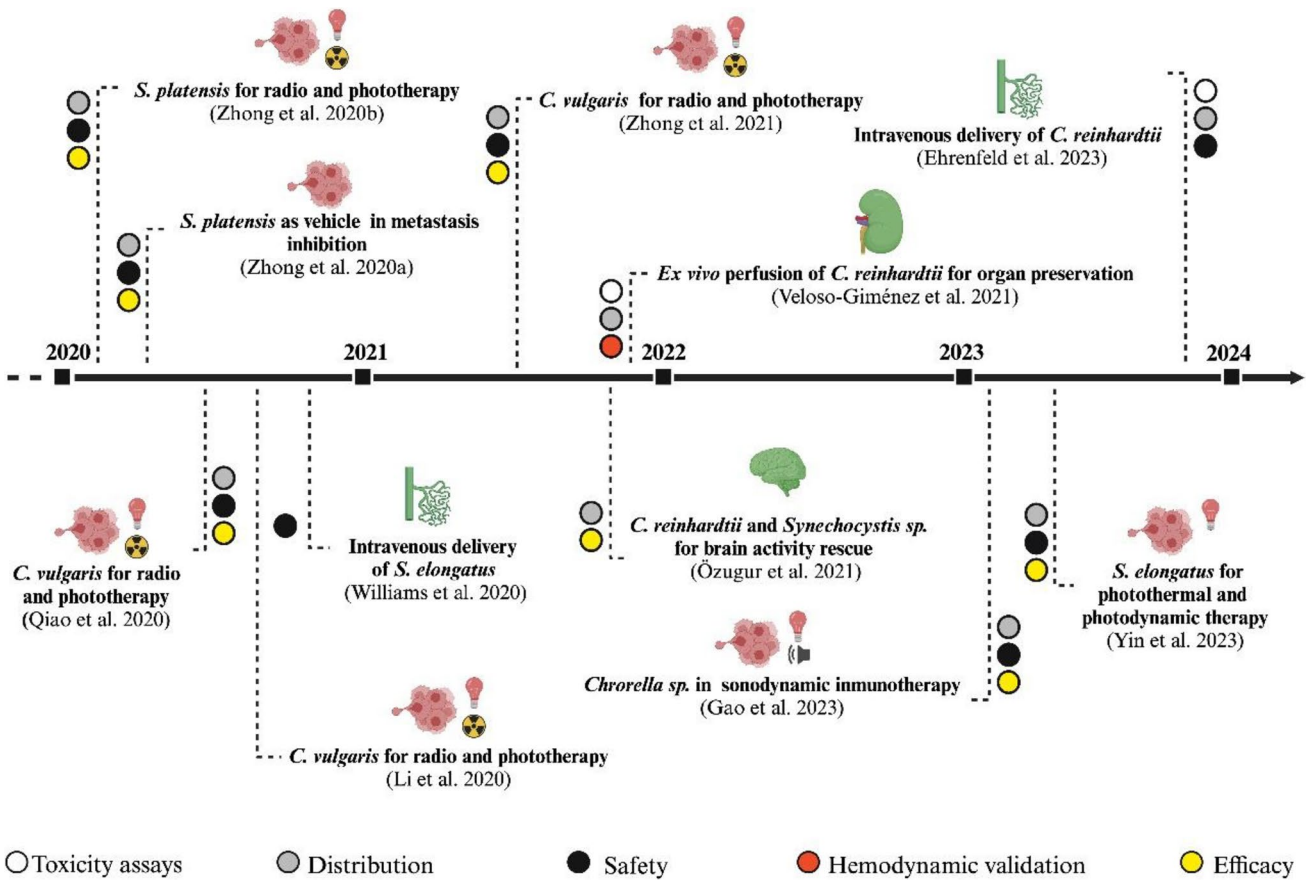

Fig. 1 Chronological progression of *chlorocytes* research. The timeline highlighting 11 key studies on *chlorocyte*s published from 2020 for intravascular oxygen supply. The studies are color-coded as indicated in the legend. This visual representation offers a concise overview of the research progress in this field over time, facilitating an understanding of the chronological development and categorization of studies

Lastly, it is crucial for the microorganism does not aggregate at low shear rates and not form conglomerates. Besides those hemodynamic issues, the interaction of *chlorocytes* with other circulating cells may pose a significant challenge, especially regarding the immune system and platelets, which must allow for an appropriate host response while ensuring the survival of *chlorocytes* in circulation. Finally, several aspects need to be considered regarding *chlorocyte*' clearance from the circulatory system.

In addition to biological concerns, fundamental technological problems should also be solved. Among them, providing adequate illumination for efficient photosynthesis to the *chlorocytes* inside the vessels of solid tissues and large organs within the body may be more complicated than expected. As described in previous sections, successful photosynthetic therapies have been applied to superficial tissues, like skin wounds or subdermal tumors, where illumination is more straightforward. However, the low tissue penetration of visible light limits its application in internal organs (Ash et al. 2017). For instance, a LED-based device was designed to illuminate arrangements of pancreas implants and microorganisms in a controlled space (Evron et al. 2014), but that approach seems unsuitable for circulating *chlorocytes*. Furthermore, in an exploratory work, cardiac intraparenchymal injections of cyanobacteria were conducted in small rodents, where tissue illumination was feasible given light exposure through the open chest and the small size of the organ (Cohen et al. 2017). Thus, scaling up to human-sized organs is a challenging problem to underscore. Additionally, the low penetration of visible light will jeopardize effective energy transmission from the surface into capillary-dwelling *chlorocytes* beyond the first millimeters of tissue. As a follow-up, upconversion nanoparticles, which convert low-energy photons into higher-energy ones, in combination with near-infrared light exposure, have been successfully employed to increase the availability of visible light inside tissues (Wang et al. 2021a; Liu et al. 2022; Gou et al. 2021), inhibiting the growth of hepatocarcinoma in a larger animal model, such as rabbit (Wang et al. 2022b). Apart from the illumination devices themselves, it is relevant to mention that the effects of irradiating internal organs with light have been poorly studied and could be a potential limitation for the clinical impact of *chlorocytes*. Additionally, the optical properties of most inner organs are not well described; thus, the illumination settings need to be refined according to data that has yet to be reported on light transmission and phototoxicity.

Regarding the potential phototoxic effects of light on tissues, it would be interesting to explore biomimetic approaches to leverage nature's protective mechanisms, drawing inspiration from various organisms exposed to high levels of radiation. This could, for instance, involve the study of natural protective pigments such as melanin, mimicking the mechanisms employed by organisms to shield themselves from harmful radiation (Araújo et al. 2014; Solano 2020). However, in contrast to those, the ideal photoprotective pigment should filter only non-photosynthetic or short wavelengths, enabling the protection of tissues while facilitating photosynthetic oxygenation. Another possibility would be the use of pigments like carotenoids and polyphenols such as flavonoids, which are known for absorbing and dissipating excess light energy, thereby reducing the risk of photodamage (Rietjens et al. 2002; Stahl & Sies 2007; Anbualakan et al. 2022). Additionally, the use of antioxidants, such as vitamins C and E (Johnson et al. 2003; Coulter et al. 2006; Sytařová et al. 2020), and compounds like glutathione, which scavenge reactive oxygen species generated by light exposure (Noctor et al. 2012; Dorion et al. 2021), could help mitigate oxidative stress-mediated tissue damage. Furthermore, exploring the utilization of longer wavelengths of light, such as red or infrared light, which penetrate deeper into tissues and are less likely to induce phototoxicity (Raza et al. 2019; Swamy et al. 2020), could be done by taking advantage of photosynthetic pigments that capture those light wavelengths in some microorganisms. Examples are the far-red-absorbing chlorophylls d and f expressed in cyanobacteria that thrive in environments with limited light availability (Wolf & Blankenship 2019; Elias, Oliver & Croce, 2024). Studies have demonstrated that the synthesis of those chlorophylls can be induced in several cyanobacteria strains by growing them under far-red light conditions (Gan et al. 2014, 2015). The use of fluorescent carbon nanomaterials may also be an option to provide active photosynthetic light. For instance, red-emitting carbon nanomaterials have been employed in bioimaging applications, demonstrating low toxicity, minimal photodamage, and deep tissue penetration (Mandal et al. 2023).

The challenges described above may represent only a few of the issues to be addressed; however, several aspects contribute to an optimistic approach to overcome them. Firstly, the enormous biodiversity and widespread presence of microalgae and cyanobacteria offer a unique opportunity to explore possible candidates for functional *chlorocytes*. In fact, approximately 40,000 microalgae species (Khan et al. 2018) and an estimated 60,000 species of cyanobacteria (Nabout et al. 2013) have been described as inhabiting marine and freshwater environments. These species live in a broad range of osmolarities (ranging from about 1 to 1000 mOsm/kg) and optimal temperatures, typically between 25 and 35 °C for cyanobacteria (Rai et al. 2016) and 15–30 °C for microalgae (Gao et al. 2023b), although some species can thrive in temperatures ranging from 30 to 40 °C, as observed in cases like *Chlorella sp.* (Pawlita-Posmyk et al. 2018) and *S. elongatus* (Yu et al. 2015). This diversity fully encompasses some necessary physiological conditions of the blood. Similarly, a broad range of sizes can also be observed for both types of photosynthetic microorganisms,

with some of the smallest cyanobacteria being between 0.2 and 2 µm in diameter (picocyanobacteria like *Prochlorococcus*), potentially enabling them to circulate within the ~ 5 µm capillary lumen. Nevertheless, before their biomedical use, essential research efforts must be made to implement novel microorganism culture protocols to enable the growth of several promising photosynthetic microorganisms in axenic conditions (Lavin et al. 2008).

Another promising aspect that may propel the establishment of *chlorocytes* as a therapeutic approach is their compatibility to serve as a vehicle for molecular tools, allowing for potential tailoring of critical aspects and properties through gene modification. In fact, in the last 10 years, novel gene expression tools have been established in some microalgae and cyanobacteria strains, and they could potentially be used for biomedical applications. Examples of these tools comprise the design of promoters, expression of stress-resistance genes, and overexpression of native metabolites. Some interesting studies are the development of modulable promoters responsive to blue light in *C. reinhardtii* (Chen et al. 2023b) and the development of novel methodologies to adapt cyanobacterial photosynthesis to stress of combined high light and high temperature (Sun et al. 2023).

Additionally, engineering metabolic pathways in cyanobacteria and microalgae have been described to produce functional metabolites, especially for implementation in the biodiesel (Rautela et al. 2024; Xue et al. 2020) and food industry (Ferreira et al. 2021), along with applications in biomedicine (McCauley et al. 2022), such as the release of recombinant growth factors and other bioactive proteins. In this regard, the genetic modification of microalgae like *C. reinhardtii* has been explored to produce recombinant proteins such as antibodies (Almaraz-Delgado et al. 2014; Munjal et al. 2014), enzymes like kallikrein (Chen et al. 2018), and human growth factors, such as vascular endothelial growth factor (Chávez et al. 2016), human interferon alpha (El-Ayouty et al. 2019), human epidermal growth factor (Baier et al. 2018), and other factors with pro-regenerative features (Centeno-Cerdas et al. 2018; Jarquín-Cordero et al. 2020). Along with this, the photosynthetic production of metabolites, such as hyaluronic acid in *Synechococcus sp.* (Chávez et al. 2021) and mannitol in *S. elongatus* (Pritam et al. 2023), has been studied, obtaining a higher yield than the one reported for many bacteria, which is potentially helpful for the chemical, medical, pharmaceutical, and food industries. In addition to recombinant molecules, some native peptides have garnered attention in this field because of their diverse bioactive properties, which can be harnessed to promote human health. These peptides exhibit a wide range of activities that hold promise for intervening in various abnormal health conditions like hypertension, hyperlipidemia, inflammation, diabetes, cancer, microbial infection, and immune disorders (Udenigwe 2014).

In exploring *chlorocytes* for medical applications, significant challenges emerge alongside promising opportunities. While initial research yields positive findings in rheological properties and short-term endothelial interactions, long-term effects on endothelial integrity and circulation pose substantial concerns. Technological hurdles, such as providing adequate illumination for *chlorocytes* within tissues, also complicate progress. However, the diversity of microalgae and cyanobacteria offers potential candidates, and advances in molecular tools hold promise for tailored modifications. Despite obstacles, *chlorocytes* have the potential to revolutionize medical therapies, addressing critical healthcare challenges through interdisciplinary collaboration and innovative research.

Clinical impact and perspectives

Before implementing *chlorocyte*-based therapies for long-term applications, such as cardiac or pulmonary insufficiencies, it will be essential to gather valuable information from acute interventions like surgical bleeding or respiratory failure, which will provide key insights towards therapeutic intravascular photosynthesis.

As already discussed, given the exponential growth of research studies in tumor treatment and the profound impact of cancer in modern societies, the establishment of intravascular photosynthetic treatments holds significant promise in this field. In this case, localized photooxidative damage may be desirable for clinical efficacy in tumor suppression or retrieval; however, the worries about potential deleterious effects of *chlorocytes* on vascular structure are shared with their use in other applications.

Among the multiple potential clinical applications described in the previous sections, it is foreseeable that the initial impact of *chlorocytes* will occur in scenarios where its implementation will be facilitated by a combination of existing technologies and accessibility to tissues and organs. In this regard, organ preservation represents an excellent candidate to pioneer this field because, when isolated from the rest of the system, organs are more amenable to manipulation in terms of illumination and perfusion. Moreover, as standard procurement procedures remove the organ's blood, this reduces potential harmful interactions between *chlorocytes* and blood cells. Additionally, well-established technologies are currently available for ex situ organ perfusion, including *chlorocyte* removal before transplantation, allowing detailed monitoring and control over the system (López-Martínez, Simón & Santamaría, 2024; Longchamp et al. 2024). Similarly, based on already established successful photodynamic therapies, multiple applications for skin disorders can be envisioned, such as intravascular oxygenation of dermal tumors and treatment of ischemic wounds.

In addition to feasibility, the potential impact on the population requirements will also guide further technological efforts in the field of *chlorocyte* biology. Blood substitutes for transfusion stand out as a procedure that could significantly benefit from this concept, as it is routinely performed in most hospitals worldwide, aiding millions of patients per year, from newborns to elderly patients. Although blood transfusion has saved countless lives, its use is associated with several critical issues, including potential adverse reactions, disease transmission, and lack of availability. Additionally, its inherent complexity, along with issues related to preservation and expiration, make this procedure highly expensive and unaffordable for some populations. Finally, the clinical impact of blood transfusions is also limited for an important number of people who reject this procedure due to cultural views.

Finally, significant translational issues must be addressed before implementing intravascular photosynthesis as a novel therapeutic approach in patients. One such concern is the absence of regulation for the intravascular administration of microorganisms as therapeutic agents, which may diminish its clinical impact, particularly regarding the potential long-term effects of such non-canonical treatment. Furthermore, from a biotechnological standpoint, the scale-up and production of *chlorocytes* must transition from proof-of-concept research settings to the development of cost-effective and scalable manufacturing processes, including logistical challenges. Lastly, the advancement of this transformative technology may provoke ethical and social concerns that could affect its translation, such as religious perspectives and apprehensions regarding physiological human enhancement for non-clinical purposes. To overcome these hurdles, this review emphasizes the need to foster and strengthen interdisciplinary collaboration among scientists, engineers, clinicians, and regulatory authorities.

Conclusions

Animals are fully dependent on oxygen produced via photosynthesis to survive. Although this dependency has been studied for centuries, only recently it has been proposed that the induction of symbiotic relationships between human tissues and photosynthetic cells could have a significant impact on human medicine and physiology. Here, various groups worldwide have provided key scientific data about the safety and efficacy of this approach, supporting its potential clinical use for the treatment of various hypoxic conditions. As oxygen is distributed in the body through the cardiorespiratory system, vasculature represents a key tissue target for human photosynthesis.

Several interdisciplinary challenges need to be addressed for the establishment of protocols to ensure circulating cells with the capacity to constantly produce oxygen and remove carbon dioxide in the intravascular space, especially regarding their biocompatibility and the development of novel illumination devices. However, these so-called *chlorocytes* may represent a big step towards human photosynthesis and, therefore, a game changer for human health.

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