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Oxygen-Releasing Biomaterials: Current Challenges and Future Applications

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Abstract

Oxygen is essential for the survival, function, and fate of mammalian cells. Oxygen tension controls cellular behaviour via metabolic programming, which in turn controls tissue regeneration, stem cell differentiation, drug metabolism, and numerous pathologies. Thus, oxygen-releasing biomaterials represent a novel and unique strategy to gain control over a variety of *in vivo* processes. Consequently, numerous oxygen-generating or carrying materials have been developed in recent years, which offer innovative solutions in the field of drug efficiency, regenerative medicine, and engineered living systems. In this review, we discuss the latest trends, highlight current challenges and solutions, and provide a future perspective on the field of oxygen-releasing materials.

The Effect of Oxygen Tension on Cellular Metabolism and Behaviour

Oxygen is an essential metabolite for the survival and function of aerobic organisms. A key role of oxygen in the human body is the oxidation of nutrients, which enables efficient energy production. For example, oxygen is required for aerobic respiration, in which a single molecule of glucose is metabolised to produce approximately 30 molecules of ATP, which is the main biomolecule for energy transfer. In contrast, anaerobic (see Glossary) respiration results in the production of only two molecules of ATP [1]. Therefore, limited oxygen availability, such as in poorly vascularised microenvironments, can lead to limited ATP availability. This in turn induces metabolic stress, formation of reactive oxygen species (ROS), and autophagy, which eventually causes cell death via apoptosis and necrosis [2–4].

Conflicts of Interest
The authors declare no conflict of interest.

Moreover, when the partial pressure of oxygen (pO_2) of a tissue falls to <5% oxygen, the tissue becomes hypoxic, which potently influences cellular signalling pathways that significantly alter cellular function. For example, hypoxia-induced alteration in activity of hypoxia-inducible factors 1, 2α (HIF-1α and HIF-2α; Figure 1) and nuclear factor kappa B results in changed expression of >100 genes that are involved in erythropoiesis, angiogenesis, cell migration, inflammation, apoptosis, cell motility, and proliferation (Box 1) [2,5–10].

The pO_2 within healthy tissues, also named physioxia, is relatively stable because it is required to maintain homeostasis. However, pO_2 levels vary significantly between the different tissues in the human body. pO_2 values can be as high as 100 mmHg in arterial blood and 70 mmHg in kidney and as low as 20 mmHg in cartilage [11–13]. Regardless, the pO_2 pressure of a tissue can be severely disturbed by pathological conditions, such as disturbed blood flow, inflammation, or an increase in tissue mass, which occur in tissue trauma, cancer, diabetes, stroke, and coronary heart disease, among others (Figure 1) [11]. While in the short term, this shift toward hypoxia associates with regenerative responses, such as neovasculogenesis, stem cell differentiation, and tissue regeneration, prolonged hypoxia associates with adverse effects, such as slowed healing, ischaemic heart disease, pulmonary hypertension, cerebral ischaemia, loss of hepatic metabolic function, systemic inflammatory response, liver fibrosis, cystic fibrosis, glaucoma, arthritis, and tissue necrosis [7,14–17]. Consequently, gaining control over the local pO_2 *in vivo* can stimulate tissue regeneration and mitigate severe adverse effects on tissue structure and organ function; thus, this represents a potent yet largely unexplored therapeutic avenue for a variety of diseases. Moreover, oxygen diffusion within implanted tissues is limited to only ~200 μm [18], resulting in severe oxygen deficiencies in the core of implanted tissues. Therefore, implant vascularisation is essential to overcome oxygen diffusion limitations, but this is a slow process, with only 5 mm of vascular penetration in 25 days into porous implanted scaffolds [19], during which implant viability needs to be maintained.

In recent years, various materials have been developed that offer a gradual and consistent release of oxygen over time [20,21]. There are two main classes of oxygen-releasing biomaterials: oxygen-carrying biomaterials (OCBs) and oxygen-generating biomaterials (OGBs). In this review, we provide a critical, comparative, and comprehensive analysis of the advantages, drawbacks, and mechanisms of oxygen release for each class, highlight suitable areas of application in the biotechnology field, and discuss anticipated future development.

Key Methods of Oxygen Generation

Multiple material fabrication strategies have been investigated for the production of OCBs and OGBs (Figure 2, Key Figure). Haemoglobin-based oxygen carriers (HBOCs), perfluorocarbons (PFCs), and peroxides have been topics of interest for over a decade, while novel technologies, such as lipid-based oxygen microbubbles (LOMs), oxygen-laden nanosponges (NSPs), hydrophobic oxygen generators (HOGs), metallic nanoparticles (NPs), and photosynthetic algae have only been explored in the recent past. Here, we discuss the various OCB and OGB biomaterials and provide the first comprehensive overview of

their respective theoretical maximum payload and their empirically observed maximum oxygen-release duration.

Oxygen-Carrying Biomaterials

HBOCs use natural haemoglobin (Hb) or myoglobin to reversibly bind oxygen. The haem group within these molecules can bind oxygen, and the extent of oxygen loading is dependent on the pO_2 (Figure 2A). Hb and myoglobin are often encapsulated within biocompatible polymeric carriers (e.g., conjugated polymers or liposomal NPs) to enhance their stability and vascular residence time [22–24]. Despite delivering a proof-of-principle and initial success in improving the pO_2 of blood, the tested formulations have often been associated with severe adverse effects, and short durations and inaccurate control over oxygen release. Most notably, owing to the production of Hb derivates, such as methaemoglobin and ferryl Hb, these formulations can significantly increase the mortality rate and myocardial infarction in multiple patient cohorts [25,26]. To address this challenge, polydopamine-coated Hb (Hb-PDA) NPs were designed by Wang and colleagues [23]. In this work, Hb-PDA NPs were developed with decreased production of Hb derivatives, which reduced cytotoxicity, increased biocompatibility, and demonstrated effective scavenging of free radicals and ROS.

PFCs have attracted much attention for their ability to serve as potential artificial blood substitutes due to their chemical and biological inertness, ease of sterilisation, and high oxygen solubility [27]. Similar to HBOCs, oxygen loading in PFCs is dependent on the pO_2 (Figure 2B). In blood, oxygen extraction from PFC emulsions can reach 90% of oxygen content [28]. However, oxygen release can also be controlled by external stimuli, such as irradiation for photodynamic therapy (PDT) [29]. Niu and colleagues used PFC-containing *N*-isopropylacrylamide-based hydrogels to enhance cell survival by preventing occurrence of anoxia in hydrogels [30]. The hydrogels had higher oxygen levels and promoted the survival and proliferation of mesenchymal stem cells (MSCs). Yet, the duration of oxygen release remained relatively short and the control over the oxygen release was poor [29].

Cyclodextrin NSPs saturated with oxygen (Figure 2C) provide a relatively novel method for oxygen delivery [31,32]. Cavalli and colleagues developed three different cyclodextrin NSPs, which were all able to entrap and release oxygen for approximately 1 h [31]. The rate of oxygen release could be enhanced using ultrasound as an external stimulus, which increased the oxygen permeation through the NSPs *in vitro*. Recently, Femminò and colleagues showed sustained release of oxygen in cyclodextrin nanospheres for >2 days, resulting in a higher cell viability under anoxic conditions compared with the control group [32].

LOMs comprise an oxygen-laden core with a monolayer shell, which can be readily conjugated with a surfactant [i.e., poly(ethylene glycol)], to increase stability (Figure 2D). LOMs have been proposed as a new route of intravenously injectable materials to address hypoxaemia because they can transport and release oxygen through the bloodstream for short periods of time [33,34]. However, LOMs with the ability to deliver a clinically meaningful amount of oxygen typically caused adverse effects due to altered

haemodynamics following systemic introduction [33]. To overcome this challenge, Peng and colleagues used interfacial nanoprecipitation to manufacture and investigate a microbubble-based intravenous oxygen carrier, which improved the survival rate of pathologic animal models with asphyxial cardiac arrest [35].

Oxygen-Generating Biomaterials

Liquid peroxides, such as hydrogen peroxide (H_2O_2), decompose into water and oxygen, thereby offering a mechanism of oxygen generation (Figure 2E). They have a fast-paced oxygen release rate due to their high water solubility and decomposition rate [36]. To increase the maximal oxygen payload and allow for more gradual release of oxygen, solid peroxides (SPs) have been explored as a way to generate oxygen by producing H_2O_2 as an intermediate product following their hydrolysis (Figure 2F). The three most commonly explored SPs are calcium peroxide (CPO), magnesium peroxide (MPO), and sodium percarbonate (SPC) [37–41]. The extent and duration of oxygen release can be tailored by tuning other factors, such as temperature, solubility, pH, and catalysts [42,43]. Initial studies showed oxygen release from peroxides up to several days, but this was associated with severe cytotoxicity because high levels of H_2O_2 and ROS are still being formed owing to the fast-paced hydrolysis of SPs. To address this challenge, both liquid peroxides and SPs are being encapsulated in a hydrophobic material [e.g., poly (caprolactone) (PCL) or poly(lactic-co-glycolic acid) (PLGA)] [38,44,45] or an enzyme-modulated material [poly(1,3-trimethylene carbonate)] [46] to control their hydrolysis rate by limiting their exposure to water molecules. These HOGs offer prolonged and gradual release rates for H_2O_2 and, thus, oxygen, which significantly decreases the cytotoxicity of SPs due to minimised accumulation of peroxide- and free radical-based toxic compounds [38,44–48]. Although this approach has been proven effective for a low concentration (<1%) of HOGs in living tissues, higher concentrations of HOGs still associate with substantial levels of cytotoxicity. Consequently, catalysts that accelerate the decomposition of H_2O_2, such as catalase and magnesium dioxide, have been found to be effective in further lowering the cytotoxicity of solid SPs [41,42,44,49,50].

An alternative peroxide-based strategy to generate oxygen involves the decomposition of various aromatic molecules (e.g., naphthalene and 2-pyridones) into endoperoxides (EPs). These constructs generate singlet oxygen ($^1O_2$) upon warming following a retro-Diels-Alder reaction (Figure 2G) [51]. $^1O_2$ molecules are reactive and can be harmful to living systems, thus they have been used in combination with antioxidants, such as ascorbic acid, to quench $^1O_2$. EPs can also be covalently linked to a polymer or scaffold to gain control over the rate of $^1O_2$ release [51–53]. Furthermore, EPs require a heat source (i.e., laser therapy) to generate $^1O_2$, which severely hinders their useability for numerous *in vivo* applications. Besides, the maximal therapeutic activity window of EPs is limited by their short half-life [52]. This half-life of EPs can be tuned depending on the temperature, stability, and size and steric effects of the aromatic molecules [51,52,54], with reported half-lives of only 8.5 h and 13 h [53,54]. Therefore, EPs are unlikely to be suitable for applications that require long-lasting release of $^1O_2$.

Photosynthetic algae have been generating oxygen for millions of years, and have recently been applied as OGBs. A unique advantage is their ability to generate a constant amount of oxygen owing to their mechanism of oxygenic photosynthesis (Figure 2H) [55–57]. Several research groups have used genetically engineered photosynthetic algae to generate oxygen and secrete growth factors [e.g., vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF)] to stimulate a pro-regenerative microenvironment for wound-healing purposes [56,57]. Centeno-Cerdas and colleagues showed stable oxygen release for >30 days of culture to bridge the prevascular phase *in vivo* [55]. However, because exposure to light is essential to the photosynthetic release of oxygen, the applications of these living materials are limited to areas of the human body that are naturally exposed to light (e.g., skin and, to a lesser extent, subcutaneous locations). Moreover, in-depth investigations of immune compatibility and toxicity are required to ensure the safety of this material because this strategy is based on the use of living xenogenic matter (e.g., production of phycotoxin) and has yet to be performed. Regardless, these living oxygen-generating systems could be engineered to avoid detection and subsequent clearance by the body's immune system. For example, algae can be endowed with red blood cell (RBC) membranes to reduce macrophage uptake and systemic clearance [58].

Manganese (IV) oxide (MnO_2) can be used as inorganic (nano)particles capable of scavenging H_2O_2 and releasing oxygen as a by-product (Figure 2I) [59–61]. A major advantage of these materials is their ability to significantly reduce oxidative stress while generating oxygen. These materials have primarily been used in PDT, because they can both lower H_2O_2 in tumour tissue and simultaneously improve MRI by releasing Mn^{2+} [59,61]. Manganese ferrite, another manganese-based oxygen-generating material, also generates oxygen using a similar mechanism as MnO_2 [62–64]. However, excessive concentrations of manganese-based materials can lead to cell and tissue cytotoxicity and a decrease in oxygen generation [64,65].

Comparison of Oxygen-Release and Oxygen-Generation Platforms

When comparing the theoretical maximum oxygen payload (maxO$_2$) and the duration of oxygen release of the various oxygen-releasing biomaterials, a clear trend can be observed (Figure 2J). In general, a higher theoretical maxO$_2$ closely correlates with an extended duration of oxygen release. For example, OGBs are able to theoretically achieve a higher oxygen payload and, thus, offer longer release times, with a range from several weeks up to a month [47,55,57,66]. By contrast, OCBs have significantly lower (two to four orders of magnitude) theoretical maxO$_2$, which associates with a shorter duration of oxygen release. OCBs are generally able to provide oxygen in the range from minutes to several days. Of note, while EPs and LOM-based OCBs offer a high potential oxygen payload, they still associate with the short duration of oxygen release that is typical of OCBs. Consequently, OCBs and OGBs are each suited for a distinct set of applications owing to their notable difference in maxO$_2$ capacity and release duration.

Applications of OCBs and OGBs

All OCBs and OGBs rely on a distinct oxygen-release mechanism that offers a unique set of advantages and disadvantages, which effectively dictates whether a material is suited for a specific application (Table 1). Thus, the development of an extensive variety of oxygen-releasing materials has opened a range of possibilities within the field of bioengineering. Specifically, OCBs and OGBs have been found to play a key role in multiple areas of applications (Figure 3): (i) *in vivo* implant and cell/tissue survival; (ii) OCB and OGB-induced metabolic reprogramming of cell fate and tissue function; (iii) cancer therapies; (iv) oxygen-generating and ROS-scavenging biomaterials; and (v) overcoming asphyxial cardiac arrest.

Transplant and Tissue Survival

The survival and functional performance of living implants depend on the mitigation or avoidance of anoxia because this detrimental condition induces cell death, which has historically plagued *in vivo* experimentation and cell-based therapies. In situ oxygenation offers a first-of-its kind solution to alleviate anoxia by sustaining aerobic metabolism. Studies focussing on alleviating anoxic stress have been carried out on different cell-containing transplants in different animals, including nonhuman primates.

Baharvand and colleagues developed core-shell oxygen-carrying MPs with a poly(vinylpyrrolidone)/ H_2O_2 core and a PLGA shell [44]. Co-implantation of these microparticles with pancreatic islets reduced hypoxia-induced cell dysfunction, inactivation of the HIF-1α pathway, and improved graft function (i.e., higher rate of glucose clearance restored physiological glucose levels by higher rate of glucose clearance). In two similar studies, CPO was used in small poly(dimethylsiloxane) discs that could enhance cellular viability and function of β-cells and implanted islet transplants [67,68]. Furthermore, CPO was incorporated into collagen-based cryogels that were able to improve the glycaemic control offered by implanted islets in diabetic mice [39].

In addition to islet transplantation, tissue-oxygenating strategies have been used to enhance the survival of living implants that were implanted to repair or regenerate the muscle, heart, bone, and skin. For example, Li and colleagues incorporated a H_2O_2-laden microshell in a poly(*N*-isopropylacrylamide) hydrogel to augment cardiac cell survival and cardiac differentiation under hypoxia [69]. In another study, Laurencin and Daneshmandi demonstrated that CPO/PLGA matrices could enhance the regeneration of vascularised bone by stimulating the migration of host cells to the interior of the OGB matrix, which allowed these cells to survive for >8 weeks [45]. In conclusion, OGBs offer a favourable approach to maintain cellular metabolism, and thereby enable the survival of *in vivo* tissues and living implants when prolonged periods of oxygen release are necessitated.

Oxygen-releasing materials have also been explored to improve cell survival in *ex vivo* scenarios. Barralet and colleagues used CPO- and MnO_2-based OGBs to sustain oxygen metabolism during organ preservation time, which is currently limited to several hours only. The study showed an increase in cell survival in aorta explants after 3 weeks with 96 ± 3%

of cells surviving when OGB were used compared with $9 \pm 6\%$ when conventional vascular preservation media was used [70].

Metabolic Reprogramming of Cell Fate and Tissue Function

The oxygen tension manipulates the angiogenic processes, which further govern wound healing, bone remodelling, and female reproduction, among others, in a multifaceted manner [71,72]. Although hypoxia is considered as the main inducer of angiogenesis, anoxia and prolonged hypoxia can hinder these regenerative processes [68,73]. Interestingly, the presence of oxygen can stimulate or support angiogenesis in hypoxic and injured tissues. Although the underlying mechanism is still not entirely understood, the presence of oxygen contributes to the generation of ROS, which are hypothesised to act as signalling molecules for angiogenesis (Box 2) [37,71,74–76].

Several studies have reported on the positive effect of oxygen-generating materials on angiogenesis. Chavez and colleagues incorporated *Chlamydomonas reinhardtii* microalgae into an integra dermal regeneration template for oxygenic photosynthesis [56]. This led to significantly increased VEGF expression of genetically engineered algae 2 weeks after implantation into mice. This in turn led to an increased recruitment of vascular endothelial cells and alpha smooth actin-positive vessels. Recently, Shiekh and colleagues formulated an exosome-laden oxygen-releasing cryogel that promoted the healing of infected diabetic wounds (faster wound closure, fibroblast proliferation, and increased collagen deposition) in a diabetic rat model [77]. Moreover, implantation of thiolated gelatin containing CPO as well as the application of CPO in combination with SPO in a PCL-poly (vinyl alcohol) wound patch resulted in increased oxygen-induced vascular endothelial cell infiltration, which formed capillary-like structures [37]. Chandra and colleagues showed that this wound patch increased the formation of large vessels in a full-thickness wound model in pigs after 8 weeks [38]. These experimental findings provide a proof-of-concept that oxygen generation materials have the ability to control and guide physiological processes, such as angiogenesis.

Controlling the oxygen tension locally *in vivo* also offers the possibility to steer the behaviour of the immune system by, for example, manipulating the functional performance of macrophages (Box 3). Kim and colleagues formulated a dual-responsive biomaterial that increased the oxygen content while simultaneously scavenging ROS. Specifically, they showed that manganese ferrite and ceria NP-anchored mesoporous silica NPs relieved hypoxia, reduced inflammation, and induced M2 macrophage polarisation following intra-articular administration in mouse joints [62]. While a shift towards the M2 phenotype is often regarded as beneficial owing to its anti-inflammatory consequences, other applications desire the presence of M1 macrophages. Multiple studies that focused on relieving tumour hypoxia and tumour drug resistance showed that the polarisation from tumour-associated macrophages (M2 subtype) to the M1 phenotype could increase the efficacy of chemotherapies and immunotherapies [60,78]. Thus, the ability of OCBs or OGBs to induce M2 polarisation could also yield adverse effects for a specific set of applications.

Multiple studies have also investigated the role of oxygen tension on human MSC and embryonic stem cell behaviour, which demonstrated the influence of oxygen on motility,

differentiation potential, and the secretion of angiogenic and immunomodulatory factors [79,80]. Moreover, the efficiency of iPSC reprogramming improved fourfold when adult human fibroblasts were reprogrammed under a hypoxic oxygen tension [81]. Since the physioxic oxygen tension of *in vivo* stem cell niches is <9% [80], higher *in vitro* oxygen tensions (~20%) are considered unnatural and have been shown to disturb gene expression and metabolism of various stem cells [82,83]. Despite the undisputable role of oxygen tension in stem cell development, research on the utilisation of oxygen-generating biomaterials to aid in the differentiation of stem cells has remained scarce [45,69].

Overcoming Tumour Hypoxia for Enhanced Photodynamic Therapy

Solid malignant tumours often alter their microenvironment to become hypoxic due to their high oxygen consumption, which fuels their aggressive growth. This also results in hypoxia-driven immunosuppression that can endow tumours with an increased level of drug resistance [78,84]. Thus, restrictions in the available amount of oxygen can limit the effectiveness of tumour treatments, and increasing the oxygen tension has been hypothesised as a potential strategy to resolve this clinically relevant challenge (Box 4) [85].

To relieve hypoxia-induced multidrug resistance in solid tumours, OGBs have been explored to locally increase the oxygen tension by decomposing endogenous intracellular H_2O_2 [86], which is overproduced by hypoxic tumours [87]. To this end, a few strategies based on biocompatible composite materials with low toxicity, targeted delivery, and high catalyst loading (i.e., photosensitiser) have been developed for PDT [86]. For example, MnO_2 was delivered in a hyaluronic acid NP in combination with various photosensitisers, such as indocyanine green [59], gold nanocages [87], acriflavine [61], and black phosphorus [88]. The reaction of MnO_2 with H_2O_2, which is induced upon irradiation (i.e., laser or X-ray) of the photosensitisers in tumour-bearing mice, resulted in significantly reduced tumours and even tumour eradication, whereas tumour growth in non-irradiated mice was not significantly reduced [89]. Other oxygen-generating approaches that have been explored for PDT include microalgae covered in a RBC membrane [58], haem dimer coupled to BP [90], and porous platinum NPs [84]. In a recent study, Colombani and colleagues constructed CPO-based cryogels to increase $CD4^+$ T cell and $CD8^+$ T cells to induce a shift from immunosuppression to antitumour immunity. Using an *in vivo* mouse model, this approach promoted natural killer cell infiltration and enhanced immune cell survival in the tumour microenvironment, which are both involved in the antitumour response [91].

All these various oxygen-generating approaches consistently contributed to tumour-size reduction or even eradication. Consequently, elevating the oxygen tension of a tumour towards normoxic levels offers a promising avenue to improve tumour treatments.

Multifunctional Oxygen-Generating and ROS-Scavenging Biomaterials

Although the primary and most intuitive goal of OCBs and OGBs is to elevate pO_2, other applications for these materials have been identified in which oxygen generation is considered a harmless by-product of its primary function (i.e., ROS scavenging) [23,39,42,49,92,93]. While the extremely oxidizing nature of ROS can be utilised for

increasing cytotoxicity in tumour tissue, it can be detrimental to the viability of healthy tissues, and has been found to have a major role in several pathological diseases [3,4]. Thus, multiple studies have focussed on developing (bio)materials, including OGBs, to reduce the ROS levels in living tissues.

Oxidative stress has a key role in osteoarthritis, among others, where increased ROS (i.e., peroxides, hydroxylated radicals, and nitric oxide) levels drive extracellular matrix degradation, joint inflammation, and chondrocyte death [94]. To protect cartilage from inflammation-induced oxidative stress, intra-articular injectable MnO_2 NPs were applied [49]. These were demonstrated to have a substantial retention time in the intra-articular space (at least 7 days) and, thus, allowed chondroprotection of articular cartilage in an osteoarthritic rat model. Tapeinos and colleagues developed biodegradable PLGA microspheres that were coated with type I collagen and decorated with MnO_2 NPs to protect rat fibroblast cells from oxidative stress [92]. Thermally responsive 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) hydrogels were explored to evaluate the protective effect of these hydrogels in a rat myocardial infarction/reperfusion model, resulting in significant reduction of local ROS accumulation in cardiomyocytes [95]. Moreover, the ROS-scavenging and oxygen-generating TEMPO hydrogel reduced ROS-mediated damage and maintenance of physiological cell function, shown by reduced left ventricle dilation and increased left ventricle wall thickness.

ROS have also been strongly linked to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with higher levels of ROS measured in the respiratory epithelium of hospitalised patients compared with the respiratory epithelium of healthy patients [96]. In a recent study, Qin and colleagues encapsulated catalase in a nanocapsule to reduce ROS-mediated immune responses, which were indicated by an increase in the number of leukocytes and further release of ROS and proinflammatory cytokines. The catalase-containing nanocapsules were able to repress replication of SARS-CoV-2 in rhesus macaques by downregulating leukocyte-mediated cytokine production [97].

Consequently, OGBs that operate via ROS decomposition have great therapeutic potential to mitigate the damaging oxidative stress associated with a variety of soft tissue diseases.

Synthetic RBC for *In vivo* Blood Oxygenation

OCBs, such as HBOCs and PFCs, have been widely explored as artificial RBC substitutes. The development of suitable RBC substitutes is indispensable, because they can have a vital role as an RBC alternative in case of depleted storage of blood supplies, which is an increasing problem in developing countries. Moreover, they represent a viable alternative to conventional blood transfusions, which are becoming progressively more costly due to the steadily growing list of disease (e.g., HIV, Ebola, and swine flu) detection tests that are mandated, among others [98]. Consequently, the demand for artificial blood products is rapidly increasing.

RBC substitutes have also found their way into other medical areas. For example, patients with severe and prolonged oxygen deprivation can experience asphyxial cardiac arrest.

When the oxygen in blood is being depleted, the heart stops beating, which further reduces the oxygen delivery to all vital organs. Failure to rapidly restore blood oxygen levels can lead to severe organ injury and even death within minutes. HBOCs and PFCs have been intensively investigated to restore the oxygen tension of blood, but both have been associated with severe adverse effects [25–27]. Recently, an injectable foam suspension containing self-assembling lipid-based microparticles that encapsulated gaseous oxygen were intravenously administered to increase the oxygen tension of the blood [99]. The oxygen-releasing microparticles significantly decreased the degree of hypoxaemia in rabbits, which reduced the incidence of cardiac arrest and other organ injuries compared with the control group. LOMs have also been devised to release oxygen within the bloodstream. Yet, a key limitation of using LOMs within the circulatory system is their associated risk of causing acute pulmonary vascular obstruction due to lipid shedding, resulting in the subsequent formation of large lipid aggregates [100]. Recently, dextran-acetyl-succinate LOMs were adopted to address this challenge. This material was investigated for its ability to improve the survival rate of a rodent model of asphyxial cardiac arrest. Strikingly, compared with results from control groups, all animal models survived the observation period and remained haemodynamically stable. Blood mixed with dextran-acetyl-succinate LOMs did not exhibit evidence of haemolysis or complement activation, and its coagulation profile was within the acceptable range [35].

Noticeably, restoring the oxygen tension of blood has relied almost exclusively on the use of OCBs. The exploration of OGBs could also be of interest, because they allow long-term release of oxygen without the need to recharge the RBC substitute. Moreover, OGBs offer heart–lung loop-independent blood oxygenation, which could prove advantageous for clinical scenarios in which the capacity of the lung to oxygenate blood is temporarily impaired.

Concluding Remarks and Future Perspectives

The research focus of past years has been primarily on the development of new OCBs and OGBs, which has provided the field with an extensive and versatile toolbox for local oxygenation. However, a shift in research focus is foreseen from the development of novel materials toward improving their safety, improving their control, and realizing their useability (see Outstanding Questions). The current toolbox of oxygen-releasing biomaterials offers a range of oxygen-release mechanisms, durations, payloads, and (toxic) by-products. Yet, almost all materials offer poor control over their oxygen release. Specifically, current materials intensively release oxygen (e.g., burst release), which dwindles over time. Endowing solid and liquid peroxides with a coating of hydrophobic materials (i.e., PCL or PLGA) or encapsulation of Hb in carriers (i.e., liposomal or micelles) has already enhanced the duration of oxygen release, but true controllable release of stable oxygen concentrations has remained largely unattainable. Gaining true control over oxygen generation is anticipated to offer more accurate and reliable control over local oxygen tensions and tissue behaviours. The more extensive use of smart (bio)materials that are sensitive to, for example, heat stimulation [66] or enzymatic cleavage [46], is expected. These materials could be applied as sacrificial coatings around OCBs or OGBs, which would prevent oxygen generation until they are triggered to degrade. On-demand oxygen

release, as used in PDT, where oxygen is released upon light stimulation, may also have a larger role in the coming years. Furthermore, an increase in combinations of existing tissue fabrication techniques with OGBs for middle to long-term oxygen generation is foreseen, which could be applied for printing vessel structures in scaffolds with oxygen-generating properties. Moreover, the safety of both OCBs (adverse effects) and OGBs (toxicity and oxidative by-products) can still be significantly improved, which is vital for the routine clinical use of these materials. Antioxidants (e.g., ascorbic acid), enzymes (e.g., catalase), or ROS-scavenging materials (MnO_2) are expected to have a key role in reducing ROS-mediated cytotoxicity, and to bridge the gap between *in vivo* studies and clinical use.

Given that oxygen has a central role in many pathological conditions and cellular behaviours, it is anticipated that novel areas of applications will be identified. As an example, oxygen was generated a side product of glucose-sensing enhancement, and could be used as an enhancer or quencher of sensing approaches [101]. Due to the versatility of the already developed toolbox of oxygen-releasing materials, it is likely that current materials can already offer viable solutions as a logical first step to address these new challenges. For example, OCBs have a rather short duration of oxygen release and, therefore, should primarily be used for processes demanding immediate oxygen release for a short period of time, such as temporarily relieving tumour hypoxia to enhance chemotherapeutic response, where reactive by-products can also be harnessed to increase cytotoxicity against tumour and steer macrophage polarisation from M2 to M1. By contrast, OGBs are ideal for applications that require a longer duration of oxygen release and a higher total payload. For example, bioengineering of tissues requires continued survival to ensure function and anastomosis of implanted tissues, which requires oxygen release for prolonged periods of time. Moreover, OGBs could have a relevant role in the steering of (stem) cell fate, which may take several weeks to complete.

In conclusion, research on oxygen-releasing biomaterials has notably increased in its intensity and abundancy over the past few years. To maintain the increasing impact of oxygen-releasing biomaterials, research should shift toward *in vivo* and clinical translation. In recent years, many materials have been developed and numerous novel research fields have been discovered for these materials, yielding promising results. However, gaining temporal control over oxygen release, improving the safety of the (bio)material, and selecting the right oxygen-releasing (bio)material for the right application are anticipated to be of high relevance to increase the development pace as well as to boost impactful and clinically applied solutions to oxygen deficits.

Acknowledgements

Glossary

Anaerobic

living in the absence of free oxygen.

Anastomosis

infiltration of blood vessels into an implanted scaffold or integration with the vasculature of the host.

Angiogenesis

process in which new blood vessels grow from existing vasculature.

Asphyxial cardiac arrest

cause of death induced by insufficient oxygen in the blood.

Autophagy

mechanism of a cell in which it removes its unnecessary components.

Catalase

enzyme that decomposes H_2O_2 into oxygen.

Cytokine

small protein essential in cell signalling.

Cytotoxicity

toxic to cells.

Emulsion

mixture of two liquids that are immiscible.

Erythropoiesis

process in the body for producing red blood cells.

Exosome

extracellular vesicles produced in the endosomes of cells.

Graft

tissue moved from one place to another by transplantation.

Glaucoma

eye disease that results in nerve damage and vision loss.

Haemodynamics

dynamics of blood flow.

Homeostasis

stable internal state of cells or tissues.

Hydrogel

a water-swollen crosslinked polymer network.

Hydrolysis

chemical breakdown of a substance by water.

Hypoxaemia

low level of oxygen in the blood.

Infarction

death of tissue due to insufficient blood supply.

Intra-articular

into an artery.

Intravenous

into a vein.

Ischaemia

local reduction in oxygen and nutrient availability leading to severe tissue damage.

Macrophage polarisation

process in which macrophages adopt different functions depending on extracellular signals. They can adopt a M1 phenotype, with a role in defence against pathogens, and a M2 phenotype, which regulates the repair of damaged tissue.

Metabolism

chemical reactions within a cell that are involved in keeping cells alive by converting nutrients into energy.

Necrosis

cell death caused by irreversible damage.

Neovasculogenesis

formation of new functional vascular networks.

Platelet-derived growth factor (PDGF)

growth factor with a role in, among others, cell growth and division.

Photodynamictherapy (PDT)

cancer treatment that combines drugs with light to destroy tumour cells.

Singlet oxygen ($^{1}O_{2}$)

electronically excited form of oxygen.

Solubility

ability of a substance to dissolve in a liquid.

Subcutaneous

under the skin.

Surfactant

compounds that reduce the surface tension between two phases.

Vascular endothelial growth factor (VEGF)

growth factor essential in angiogenesis.

Xenogenic

a foreign substance introduced into an organism.

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Outstanding Questions

How can control over the release of oxygen be realised to enable the release of a user-defined amount of oxygen in a manner that is stable over time?

How can the safety of various oxygen-releasing materials be improved to allow them to reach clinical approval and routine clinical use?

What are the most promising research areas for multiple OCBs and OGBs?

What are the long-term consequences of introducing oxygen-releasing materials within living implants or hosts?

Highlights

Oxygen tension is a crucial factor in many diseases, and gaining control over local partial pressure of oxygen (pO_2) using oxygen-releasing materials can have a significant role in overcoming these pathological conditions.

Novel oxygen-releasing strategies have extended the oxygen-generating window from several hours to several weeks and offer improved control over oxygen-release profiles by shifting away from pO_2-based diffusion towards biomaterial-controlled oxygen release.

Oxygen-releasing biomaterials hold potential to improve many (novel) biomedical areas, including improving *in vivo* survival of living implants, offering metabolic control over cell fate and tissue function, enhancing the effectivity of photodynamic anticancer therapies, reducing reactive oxygen species-mediated cellular damage, and acting as synthetic red blood cells (RBCs) for *in vivo* blood oxygenation.

Box 1.

Mechanism of Hypoxic Mediators HIF-1α and HIF-2α

In hypoxia, HIF-1α and HIF-2α is stabilized due to reduced prolyl hydroxylation, leading to the activation of the anaerobic metabolism for cell survival, the recruitment of new vasculature, the activation of Glut1 and glycolytic enzymes, the upregulation of the apoptotic pathway (depending on hypoxia severity) and the inhibition of mitochondrial respiration [2,6,8]. Mild hypoxia will lead to the promotion of pro-survival functions of the p53 response, while severe or continued hypoxia will lead to the p53-dependent apoptosis activation [9].

Box 2.

Physiology of Angiogenesis

All vascular cells can produce ROS through oxygen metabolism [71], which correlates with promoted signalling of, for example, VEGF, angiopoietin [75], and fibroblast growth factor [74]. Moreover, ROS facilitate the hypoxic response by decreasing prolyl hydroxylase domain protein activity, thus contributing to the stabilisation of HIF-1α [74,75]. Therefore, it has been hypothesised that oxygen-releasing materials could contribute to controlling the angiogenic process.

Box 3.

Macrophage Polarisation by Oxygen Tension

Upregulation of HIF-1α by hypoxia as well as an increase in ROS in macrophages have shown to induce an M1 phenotype, while downregulation of HIF-1α and relief of hypoxia and ROS can induce the proinflammatory M2 phenotype [113]. Therefore, OCBs and OGBs have been hypothesised to have the potential to control macrophage polarisation.

**Box 4.**

Role of Oxygen within Photodynamic Therapy

Oxygen has been shown to facilitate DNA double-strand breaks and expose cells to oxidative stresses via ROS generation [58,84,88]. Moreover, oxygen is an essential component of several anticancer therapies, such as PDT, where photosensitisers use oxygen to generate cytotoxic ROS and singlet oxygen [84] to destroy proteins and nucleic acids in tumour cells, which induces apoptosis and necrosis [93]. PDT is an important treatment modality for solid tumours owing to its minimally invasive properties, superior spatiotemporal selectivity [93], and potential to initiate an antitumour immune response [88].
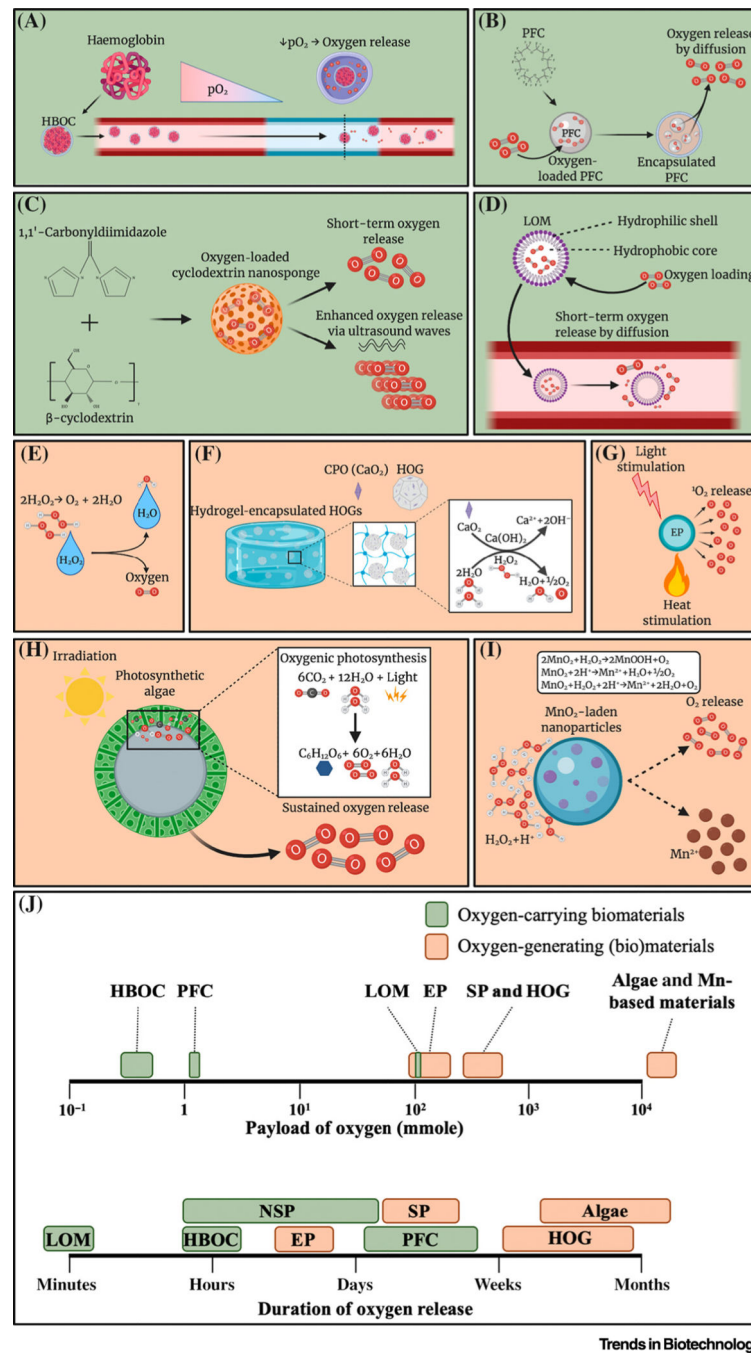
Causes of Hypoxia
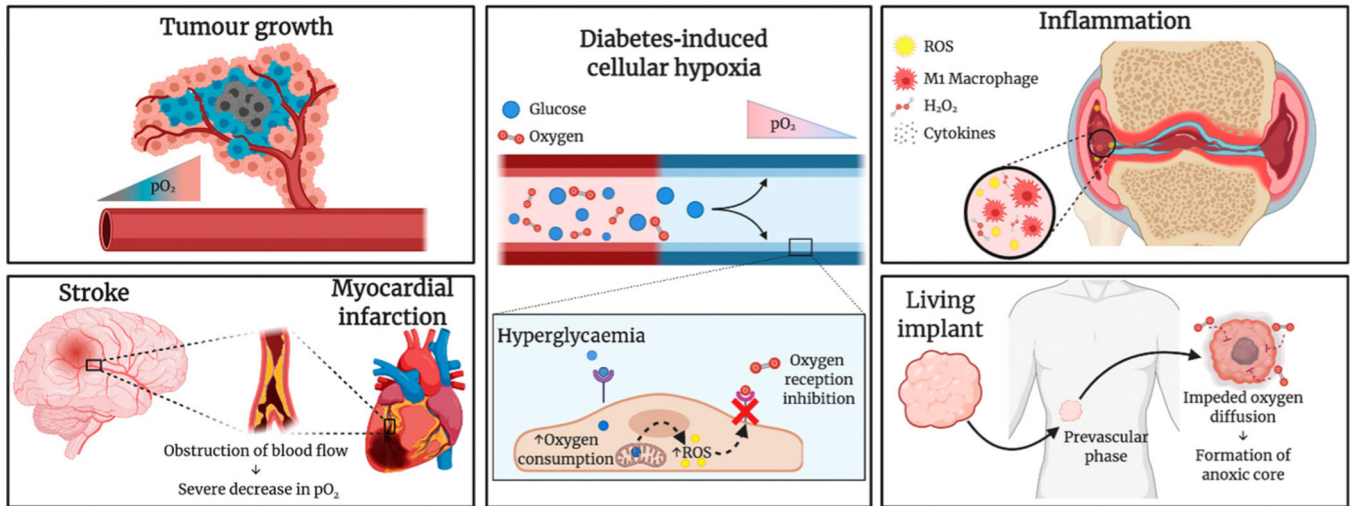
Consequences of Hypoxia
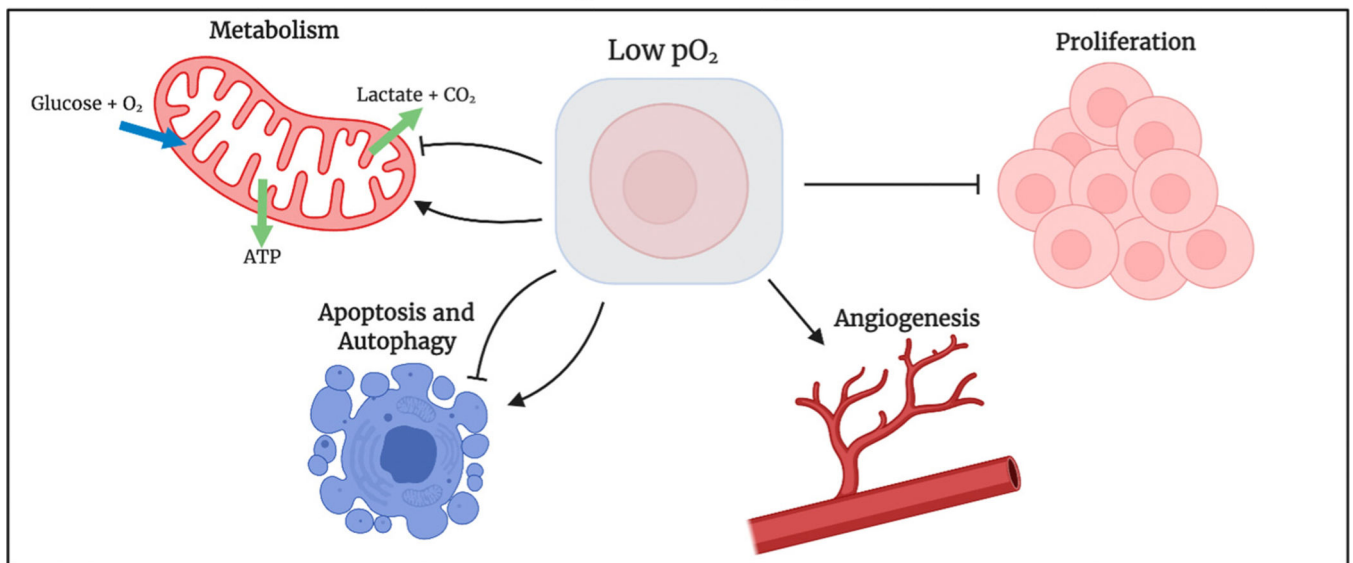
Trends in Biotechnology

Figure 1.
Schematic Overview of the Causes and Consequences of Hypoxia on Cellular Behaviour.
Abbreviations: pO_2, partial pressure of oxygen; ROS, reactive oxygen species. Figure
created with BioRender.com.

Figure 2.

Key Figure Oxygen Release from Oxygen-Carrying and Oxygen-Generating Biomaterials (OCBs and OGBs)

(A–I) Oxygen-release mechanism of various OCBs and OGBs: (A) haemoglobin-based oxygen carrier (HBOC), (B) perfluorocarbon (PFC), (C) nanosponge, (D) lipid-based oxygen microbubble, (E) liquid peroxide, (F) solid peroxide (SP), (G) endoperoxide, (H) algae-based biomaterials, and (I) manganese-based materials. (J) Comparison of oxygen payload [35,38,40,53,102–104] and duration of OCBs and OGBs
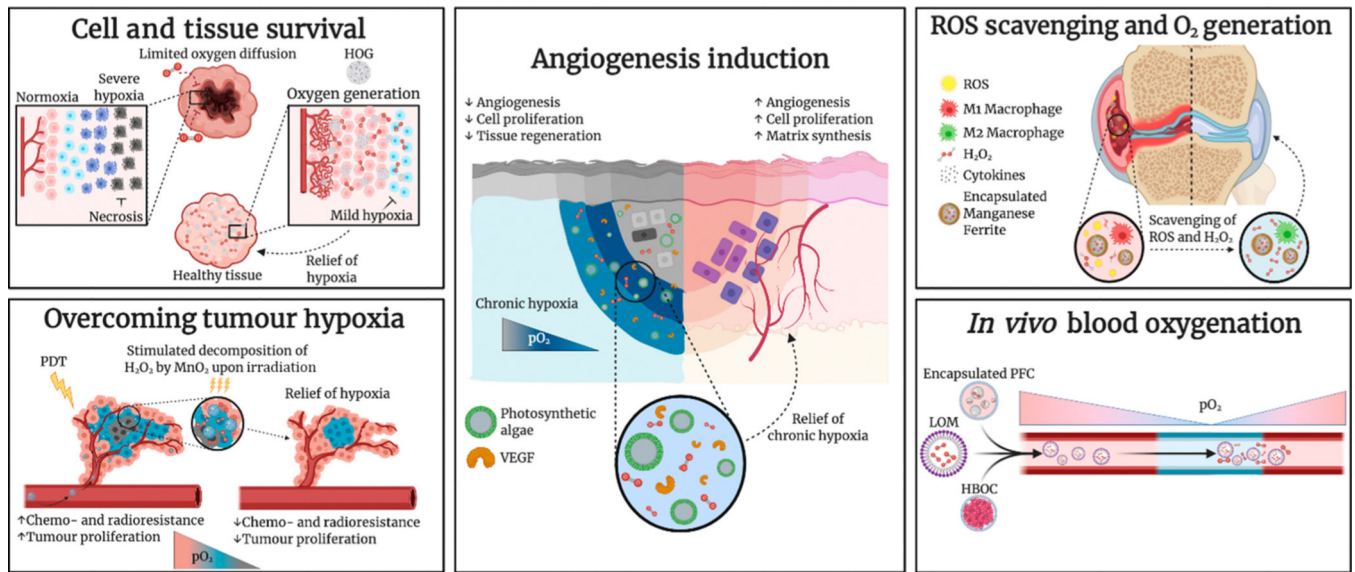
[23,24,31,32,35,37,39,47,53–55,57,66,102,105–110]. Abbreviations: $^1O_2$, Singlet oxygen; CPO, calcium peroxide; EP, endoperoxide; HOG, hydrophobic oxygen generator; LOM, lipid-based oxygen microbubble; Mn, manganese; MnO_2, manganese (IV) oxide; pO_2, partial pressure of oxygen. Figure created with BioRender.com.

Figure 3.
Research Applications of Oxygen-Carrying and Oxygen-Generating Biomaterials (OCBs and OGBs). Abbreviations: HBOC, haemoglobin-based oxygen carrier; HOG, hydrophobic oxygen generator; LOM, lipid-based oxygen microbubble; MnO_2, manganese (IV) oxide; PDT, photodynamic therapy; PFC, perfluorocarbon; pO_2, partial pressure of oxygen; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor. Figure created with BioRender.com.

Table 1.

Advantages and Drawbacks of Various Oxygen-Releasing Biomaterials

Method	Mechanism	Advantages	Drawbacks	Refs
Oxygen-carrying biomaterial				
HBOC	Binding of oxygen with haem groups	Use of natural human protein (i.e., Hb) Enhanced stability of encapsulated Hb Encapsulation of higher amounts of Hb compared with RBCs Long shelf life	Short half-life (and oxygen release) in blood circulation Binding of Hb to nitric oxide (can result in vasoconstriction) Oxidative damage by increase of free radicals, causing adverse effects	[23,24,111]
PFC	Dissolving oxygen in oil via Van der Waals forces	Does not require blood-type matching May be used as contrast agents with MRI Low cost Long shelf life	Rapid plasma clearance Low oxygen-carrying ability at physiological oxygen levels Induces flu-like symptoms Can bind to nitric oxide (which may result in vasoconstriction) Causes severe adverse effects	[105–107,112]
NSP	Binding of oxygen to cyclodextrins	Oxygen release can be enhanced externally (offers more control) Biocompatible, biodegradable, and nontoxic	Short release times of oxygen limits applicability Needs external stimulus for enhanced oxygen generation	[31,32]
LOM	Encapsulation of gaseous oxygen in microbubbles	Can be used as contrast agents for ultrasound imaging Lipid bubble increases oxygen-loading capacity Able to release high amounts of oxygen in short time	Short release times of oxygen Often have relatively large sizes ($> 10\mu m$) Limited shelf life Can cause adverse haemodynamic effects	[33,35,110]
Oxygen-generating biomaterials				
Liquid peroxides	Decomposition of H_2O_2	Faster oxygen release due to higher solubility in water Can be bound to high-molecular-weight polymers to tailor oxygen generation Catalysts can be used to catalyse reaction	Catalyst needed to lower cytotoxic effect of H_2O_2 and ROS Hard to control release rate and burst release	[36]
SP	Generation and decomposition of H_2O_2	Ease of use High payload CPO: high purity for sustained release SPC: biocompatible products MPO: slowest oxygen formation	Hard to control release rate and burst release Catalyst needed to lower cytotoxic effects of by-products By-products (e.g., calcium hydroxide) increase local pH CPO: lowest solubility SPC: less purity MPO: less purity	[39,43]
HOG	Generation and decomposition of H_2O_2 in microparticles	Ease of use Better control over oxygen release Extended release duration High payload	Catalyst needed to lower cytotoxic effects of by-products	[38,44,45,47]
EP	Decomposition of aromatic molecules in endoperoxides to generate $^1O_2$	No cytotoxic by-products Can be linked to polymer or scaffold to control oxygen release	Toxic main product ($^1O_2$) Requires energy (e.g., heat) to generate $^1O_2$ Long treatment times needed for effective therapeutic treatment Short half-life	[51–54]
Algae-based biomaterials	Oxygenic photosynthesis	Theoretically infinite oxygen production Can be genetically engineered to secrete growth factors	Limited applications due to required light exposure Not extensively tested *in vivo* for safety Likely not immunocompatible	[55–58]
Mn-based materials	Catalysed decomposition of H_2O_2	Lower ROS-related cytotoxicity Enhanced MRI performance due to reduction of MnO_2 into Mn^{2+}	Oxygen release dependent on H_2O_2-rich environments More extensive (human) *in vivo* studies needed to determine safety Excessive Mn^{2+} can lead to oxidative damage in liver	[60,62,65]