Chapter

Applications of Oxidoreductases

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Abstract

Oxidoreductases comprise of a large group of enzymes catalyzing the transfer of electrons from an electron donor to an electron acceptor molecule, commonly taking nicotinamide adenine dinucleotide phosphate (NADP) or nicotinamide adenine dinucleotide (NAD) as cofactors. Research on the potential applications of oxidoreductases on the growth of oxidoreductase-based diagnostic tests and better biosensors, in the design of inventive systems for crucial coenzymes regeneration, and in the creation of oxidoreductase-based approaches for synthesis of polymers and oxyfunctionalized organic substrates have made great progress. This chapter focuses on biocatalytic applications of oxidoreductases, since many chemical and biochemical transformations involve oxidation/reduction processes, developing practical applications of oxidoreductases has long been a significant target in biotechnology. Oxidoreductases are appropriate catalysts owing to their biodegradability, specificity and efficiency and may be employed as improved biocatalysts to substitute the toxic/expensive chemicals, save on energy/resources consumption, generate novel functionalities, or reduce complicated impacts on environment.

Keywords: oxidoreductases, cofactors, biosensors, coenzymes regeneration, biocatalytic

1. Introduction

The various chemical transformations catalyzed by enzymes make these catalysts a key goal for utilization by the promising biotechnology industries. In the recent years, intense research in the field of enzyme technology has provided numerous approaches that facilitate the practical application of enzymes. This chapter emphasizes the application of oxidoreductases which catalyze the exchange of electrons amid the donor and acceptor molecules, in reactions involving electron transfer, proton/hydrogen extraction, hydride transfer, oxygen insertion, or other imperative steps. Oxidoreductases acquire advantage from the inclusion of different cofactors - for instance heme, flavin and metal ions - to catalyze redox reactions [1]. Majority of oxidoreductases are nicotinamide cofactor-dependent enzymes which have a high preference for nicotinamide adenine dinucleotide phosphate (NADP) or nicotinamide adenine dinucleotide (NAD) and they are further classified in six major classes which are oxidases, dehydrogenases, hydroxylases, oxygenases, peroxidases and reductases [2]. This chapter demonstrates the potential applications of oxidoreductases on the growth of oxidoreductase-based diagnostic tests and better biosensors, in the design of inventive systems for crucial coenzymes regeneration, and in the formation of oxidoreductase-based approaches for synthesis of polymers and oxyfunctionalized organic substrates.

2. Oxidoreductase-based diagnostic tests and as biosensors

The diagnosis and monitoring of a variety of diseases is extremely demanding nowadays for routine examination of clinical samples and other associated tests. The diagnostic enzymes are used for the detection/diagnosis or prognosis of disease conditions due to their substrate specificity and quantitated activity in the presence of other proteins, and are preferred in diagnosis, which can be used as a diagnostic tool for disease detection [3]. Depending on the verity of the disease, diseased state often leads to tissue damage. In such conditions, enzymes specific to diseased organs are released into blood circulation with augmented enzyme activity. The measurement of corresponding enzyme activities in blood/plasma, or any other body fluid, has been exploited in the diagnosis of diseased tissues/organs [3].

Jixu Wang et al. [4] investigated the expression and significance of glucose-6-phosphate dehydrogenase (G6PD) in human gastric cancer progression and prognosis. Apoptosis and necrosis are two major types of cell death in normal and disease pathologies. A key signature for necrotic cells is the permeabilization of the plasma membrane which can be quantified in tissue culture settings by measuring the release of the intracellular enzyme lactate dehydrogenase (LDH). It has been described that the measuring LDH release is a useful method for the detection of necrosis [5]. Two dehydrogenases, specifically, sorbitol dehydrogenase (SDH) and LDH, are used for cancer prognosis [3]. Reports suggested that in prostate cancer [6], and precancerous colorectal neoplasms [7], an abnormal serum concentration of SDH has been observed. Additionally, an enhanced level of SDH can be observed in acute liver damage and parenchymal hepaticdiseases [3]. It has been reported that LDH, marker of anaerobic metabolism, is associated with highly invasive and metastatic breast cancer and suggested that the association of activity of LDH in tumor tissue with mammographic characteristics could help in defining aggressive breast cancers [8]. The gene expression of LDH is studied in several human malignant tumors, collectively among colorectal cancer [9], lung cancer [10–12], breast cancer [13], oral cancer [14], prostate cancer [15], germ cell cancer [16], and pancreatic cancer [17]. In recent times, the prognostic value of the serum LDH level in cancer patients has been considered as a significant area of research. Additionally, LDH performs as a prognostic marker in patients with acute leukemia [18] and sickle cell disease [19].

A biosensor is an analytical tool that comprises a biological or biologically derived sensing matter with close proximity to the physico-chemical transducer [3]. The chief function of such a device is to produce a discrete or uninterrupted signal that is comparative to the concentration of the analyte [20]. Enzyme-based chemical biosensors are based on biological recognition and in order to function, the enzymes must be accessible to catalyze a specific biochemical reaction and be stable under the normal operating circumstances of the biosensor [21]. Generally the function of oxidoreductase biosensors is dependent on charge transport amid the enzyme and an electrode surface by means of coenzymes or redox mediators [22].

Over the years, various enzyme-based biosensors have been developed, however only a few of them are commercialized. The majority of the published work on enzymatic biosensors focuses on targeted blood glucose monitoring based on amperometric techniques [3]. The earliest glucose biosensor based on glucose dehydrogenase from Erwinia sp. and carbon paste was generated by Laurinavicius et al. [23] where the enzyme was incorporated in a polylysine-albumin gel, and the anchoring material was a paste of chemically adapted carbon powder, fumed silica, and binding material. A cellulose dehydrogenase based glucose biosensor from a mutant of *Corynascus thermophilus* has been developed, and a glassy carbon electrode (GCE) was acquired

Enzymes	Analyte	Test sample	Disease diagnosed	References
Glucose oxidase	Glucose	Blood plasma, blood serum, urine, and saliva	Diabetes, hypoglycemia	[26–29]
Oxalate oxidase	Oxalate	Blood serum and urine	Idiopathic urolithiasis and various intestinal diseases	[30]
Cholesterol oxidase	Cholesterol	Blood serum	Coronary heart disease, myocardial and cerebral infarction (stroke)	[31–34]
Lactate oxidase	Lactate	Blood plasma, blood serum, drug and biological samples	Hyper lactatemia, cardiac arrest, resuscitation, sepsis, reduced renal excretion, decreased extra hepatic metabolism, intestinal infarction and lacticacidosis	[35–40]

Table 1.
Oxidoreductase enzymatic biosensors as diagnostic tools.

by direct electrode position of gold nanoparticles (AuNPs). The biosensor was used for the detection of glucose in human saliva samples, with successful results in terms of both revival and association with glucose blood levels [24]. This proposes the development of noninvasive glucose monitoring devices. The details of different oxidoreductase enzymatic biosensors applied for clinical diagnosis are listed in **Table 1**. The first marketable biosensor (glucose biosensor) was commenced in 1975 which was derived from the electrochemical recognition of hydrogen peroxide, and the glucose oxidase was employed for the improvement of the biosensor [3]. Subsequently, Clemens et al. [25] established a novel amperometric glucose biosensor in a bedside artificial pancreas, and it was marked underneath the brand name "Biostator" by Miles (Elkhart, Indiana).

3. Oxidoreductases in coenzymes regeneration

The most of oxidoreductases for catabolism and anabolism significantly require two natural nicotinamide-based coenzymes (NAD and NADP), respectively. The most NAD(P)-dependent oxidoreductases choose one coenzyme as an electron acceptor or donor to the other depending on their diverse metabolic functions [41]. Generally coenzymes are involved in these oxidoreductase-catalyzed reactions to transport electron, hydride, hydrogen, oxygen, or other atoms or small molecules in diverse enzymatic pathways [42, 43]. The nicotinamide adenine dinucleotide (NAD)/nicotinamide adenine dinucleotide phosphate (NADP), ubiquinone (CoQ), and flavin mononucleotide (FMN)/flavin adenine dinucleotide (FAD) are the typical coenzymes. Nicotinamide-based coenzymes for the electron transport and storage in the form of hydride groups are the most noteworthy in view of the fact that 80% of characterized oxidoreductases necessitate NAD as a coenzyme, and 10% of them require NADP as a coenzyme [44].

Nicotinamide coenzymes based dehydrogenases are of emergent importance for the production of chiral compounds, either by reduction of a prochiral precursor or via oxidative resolution of their racemate [45]. Nevertheless, the oxidized and reduced nicotinamide cofactors regeneration is an extremely critical step as the employ of these cofactors in stoichiometric amounts is too expensive for function. There are very few enzymes which are appropriate for the regeneration of oxidized

nicotinamide cofactors. Glutamate dehydrogenase can be utilized for the oxidation of NADH in addition to NADPH while l-lactate dehydrogenase is able to oxidize NADH only [45]. The reduction of NAD^+ is carried out by formate and FDH [45]. Glucose-6-phosphate dehydrogenase and glucose dehydrogenase are proficient to reduce both NAD^+ and $NADP^+$ [45]. It has been reported that ADH from horse liver reduces NAD^+ whereas ADHs from *Lactobacillus* strains catalyze the reduction of $NADP^+$ [45]. These enzymes can be applied by their inclusion in entire cell biotransformations by an $NAD(P)^+$-dependent major reaction to achieve *in situ* regeneration of the consumed cofactor [45]. And for the regeneration of the reduced cofactors NADH and NADPH numerous systems for instance engineered formate dehydrogenase [46, 47], phosphite dehydrogenase [48, 49], glucose dehydrogenase [50, 51] plus cosubstrate are well established and extensively used.

Johannes et al. [52] reported the engineering of a highly stable and active mutant phosphite dehydrogenase (12x-A176R PTDH) from *Pseudomonas stutzeri* and evaluation of its potential as an effective NADPH regeneration system in an enzyme membrane reactor. They have utilized two practically imperative enzymatic reactions including xylose reductase-catalyzed xylitol synthesis and alcohol dehydrogenase-catalyzed (R)-phenylethanol synthesis as models, and the mutant PTDH was compared to the commercially available $NADP^+$-specific *Pseudomonas sp*. 101 formate dehydrogenase (mut Pse-FDH) that is extensively employed for NADPH regeneration [52]. Soluble water-forming NAD(P)H oxidases comprise a promising $NAD(P)^+$ regeneration scheme since they only require oxygen as cosubstrate and produce water as only byproduct [53]. In addition, the thermodynamic equilibrium of O_2 reduction is a significant driving force for mostly energetically unfavorable biocatalytic oxidations [53]. Petschacher et al. [53] presented the generation of an NAD(P)H oxidase with high activity for both cofactors, NADH and NADPH. Applicability for cofactor regeneration is shown for coupling with alcohol dehydrogenase from *Sphyngobium yanoikuyae* for 2-heptanone production.

4. Oxidoreductase-based approaches for synthesis of polymers and various organic substrates

Enzyme catalyzed oxidation reactions have achieved growing concern in biocatalysis recently, reflected also by numerous outstanding reviews on this topic reported in the last years [54–56]. The group of oxidoreductases, to which all enzyme catalyzing oxidoreduction reactions, comprises numerous groups of biocatalysts such as dehydrogenases, monooxygenases, dioxygenases, oxidases, peroxidases, etc. [55]. Moreover, the enzymatic oxidative polymerizations have advantages of using nontoxic catalysts and mild reaction conditions, and the specific enzyme catalysis affords regio- and chemoselective polymerizations to construct functional materials [57]. It has been reported that peroxidases with the use of hydrogen peroxide as oxidant efficiently induce the oxidative coupling of phenols to phenolic polymers, the majority of which are scarcely attained by conventional chemical catalysts [57]. In addition, it has been published that laccase and peroxidase are helpful for production of cross-linked polymers such as artificial urushi and biopolymer hydrogel [57]. Kobayashi [58] established that the enzymatic polymerization as to be an efficient method of polymer synthesis. The polymerization uses hydrolases and oxidoreductases as catalysts and this new method of polymer synthesis afforded natural polysaccharides like cellulose, amylose, xylan, and chitin, and unnatural polysaccharides catalyzed by a glycosidase from well-designed monomers, varied functionalized polyesters catalyzed by lipase from a variety of monomers, and poly-aromatics materials catalyzed by an oxidoreductase

and an enzyme model complex from phenols and anilines [58]. Furthermore, vinyl polymerization has been initiated by oxidoreductase [58].

Marjanovic et al. [59] reviewed the oxidative oligomerization and polymerization of various arylamines, e.g., aniline, substituted anilines, aminonaphthalene and its derivatives, catalyzed by oxidoreductases, such as laccases and peroxidases, in aqueous, organic, and mixed aqueous organic monophasic or biphasic media. Owing to the nontoxicity of oxidoreductases and their elevated catalytic effectiveness, as well as high selectivity of enzymatic oligomerizations/polymerizations under gentle conditions by means of primarily water as a solvent and often resulting in minimal byproduct formation enzymatic oligomerizations and polymerizations of arylamines are environmentally friendly and considerably contribute to a "green" chemistry of conducting and redox-active oligomers and polymers [59].

It has been also established that oxidative enzymes comprise privileged catalysts in organic synthesis [60]. Environmentally benign reaction conditions with high selectivity are the most fascinating characteristic exhibited by these biocatalysts in contrast to classical metal-based reagents. de Gonzalo et al. [60] reviewed the new perspectives and concepts derived from oxidative enzymatic processes, involving oxidative C-C bond forming reactions, atroposelective oxidations, oxidative dynamic processes, interconnected reactions, cyclic deracemizations, oxidative desymmetrizations and artificial oxidative enzymes. Oxidoreductases comprise an imperative group of biocatalysts as they facilitate not merely the broadly used stereoselective reduction of aldehydes and ketones but also the less well exploited oxidation of alcohols and amines [53]. In addition, oxidoreductases catalyzed oxidations are utilized for production of chiral alcohols and amines by deracemization [54, 60–62]. It has been reviewed thoroughly that the oxidoreductases enable chemists to perform highly selective and efficient transformations ranging from simple alcohol oxidations to stereoselective halogenations of non-activated C-H bonds [63]. Mifsud et al. [64] demonstrated for the first time that catalytic water oxidation mediated by robust TiO_2 semiconductors can be productively coupled to oxidoreductases achieving photobiocatalytic redox reactions.

One of the major applications of oxidoreductase is a pharmaceutical synthesis of 3,4-dihydroxylphenyl alanine (DOPA), which is employed in the treatment of Parkinson's disease and the industrial process that synthesizes DOPA make use of the oxidoreductase polyphenol oxidase [65]. It has been reported that the enantioselective reduction of C-4-substituted 3,5-dixocarboxylates can be carried out by using alcohol dehydrogenase from *Lactobacillus brevis* (LBADH) over-expressed in *E. coli* [66]. Laccase can be employed to synthesize numerous complex medicinal agents including triazolo(benzo)cycloalkyl thiadiazines, vinblastine, penicillin X dimer, cephalosporin antibiotics, and dimerized vindo-line [67]. In addition laccase can be used to synthesize a range of functional organic compounds including polymers with specific mechanical/electrical/optical properties, textile dyes, cosmetic pigments, flavor agents, and pesticides [68]. Biocatalysis is facilitating technology to organic synthesis chemistry by providing high selectivity of enzymatic reactions under mild conditions makes it a very valuable tool for green chemistry.

5. Medical applications

Due to the specificity and bio-based nature, potential applications of oxidoreductases in various fields are attracting active research efforts [69]. Several products generated by oxidoreductases are finding applications as antimicrobial, detoxifying, or active personal-care agents [69]. One potential application is laccase-based *in situ* generation of iodine, a reagent extensively used as disinfectant [67]. It has been

described that laccase-iodide salt binary iodine-generating system (for sterilization) can have several advantages over the direct iodine application [69]. Peroxidases may replace laccase for the application, even though they would require H_2O_2 as cosubstrate [69]. The ClO^- and Mn(III) species formed by haloperoxidase and Mn-peroxidase are extremely effective oxidants and antimicrobial agents [70]. Peroxidase can also be used to cross-link collagen which is beneficial to the healing of damaged skin [71]. The physiological activities of lysyl oxidase comprise the extracellular matrix construction which can hasten wound-healing [72, 73]. A glucose oxidase, lactoperoxidase, and iodide system has been tested for dental care and the oxidase produces H_2O_2 to feed the peroxidase, so that it can produce iodine that can kill plaque-causing bacteria [74]. It has been reported that the haloperoxidase can be used to oxidatively modify rubber latex surfaces, making them less allergenic [75]. A secreted oxidoreductase may even be developed as a vaccine against secretor microbes such as, *Aspergillus oryzae* catalase A protein has been studied as a potential aspergillosis vaccine [69]. It has been reported that low-molecular-mass laccase purified from the mushroom *Tricholoma giganteumis* possesses significant HIV-1 reverse transcriptase inhibitory activity [76]. As nature's own catalysts, enzymes acquire very diverse specificity, reactivity, and other physicochemical, catalytic, and biological properties highly enviable for miscellaneous industrial and medical applications [69].

6. Conclusions

Tremendous progress has been made in the recent years in the field of applications of oxidoreductases. Oxidoreductases metabolism is a fundamental bioprocess that plays a pivotal role in all species, including humans, plants, animals, and microorganisms, as their specific function is to catalyze oxidation and reduction reactions that occur within the cell. Abnormality in this metabolic system leads to a number of metabolic disorders. Thus, owing to the remarkable properties of oxidoreductases, they can be used for the diagnosis of disorders. They can provide insight into the diseased state by diagnosis, prognosis, or by assessment of response therapy. It has been established that oxidoreductases as biosensors are becoming popular potential tools in biotechnology due to their high specificity. With oxidoreductases, the conversion of a variety of aliphatic/aromatic molecules can be achieved; inert hydrocarbons can be functionalized (by hydroxylation, sulfoxidation, epoxidation, etc.); regio-, enantio- (on racemic substrates); enantiotopo– (on prochiral sub-strates); and chemo-selective reactions can be accomplished; important synthons from inexpensive and renewable biomaterials can be constructed; and the negative environment impact can be reduced [69]. Since numerous chemical and biochemical transformations engage oxidation/reduction processes, developing practical biocatalytic applications of oxidoreductases has long been an imperative target in biotechnology.

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Conflict of interest

The author declares no conflict of interest.

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