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Review Article

Dioxygen and reactive oxygen species' paramagnetic properties are important factors in dermatology

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Dioxygen (the O_2 molecule) is an important component of all tissues including skin. Even small fluctuations of O_2 amount (dioxygen concentration changes in the tissue microenvironment) can strongly affect the signaling functions of cells through the reactive oxygen species (ROSs) activity and hence - the whole cellular metabolism, the cell proliferation, and differentiation, etc [1,2]. Most of these species are paramagnetic; that is, they possess internal magnetic moment [3-7]. Not many dermatology doctors are aware of these important dioxygen and ROS properties [8,9] which crucially depend on the electronic structure of such radicals and their spin interactions. Modern quantum chemistry and biophysics provide useful knowledge about spin-dependent interactions between ROS, O_2 and organic components of the cell [10]. This mini-review describes spin-dependent essential features of dioxygen and ROS involvement in some dermatology diseases, hair growth and other problems being mainly controlled by the dermal papilla, the hair follicle, psoriasis treatment and photodynamic therapy.

Introduction

Dioxygen as a small diatomic O_2 molecule differs from other chemical species by its magnetic properties. In big contrast to an overwhelming majority of chemically stable organic substances, the O_2 molecule increases its weight in magnetic balance; that is dioxygen is a paramagnetic gas, while most organic substances are diamagnetics [1-4]. Both types of species are chemically stable at ambient conditions (in the absence of fire or spark). Organic stuff as components of alive cells consists of biopolymers and molecules (proteins, lipids, sugars, DNA, RNA, adenine, guanine, glucose, etc.), all of which possess even numbers of electrons. Being paired with anti-parallel spins these electrons provide zero magnetic moments; that is why most organic substances represent diamagnetic stuff and are slightly repelled by an external magnetic field. Both diamagnetics and paramagnetic do not retain their magnetization when the external magnetic field is removed. For the late species, chaotic movement in the gas phase destroys their magnetic moment's alignment in zero fields.

Dioxygen is a stable biradical with internal magnetic moment (a paramagnetic species) because of two non-paired electrons in the O_2 valence shell with parallel spins [2,3]. The most important ROSs (the excited singlet $O_2(a^1\Delta_g)$ oxygen, superoxide $O_2^{\cdot-}$ ($X^2\Pi_g$) ion-radical, hydroxyl $OH^{\cdot}$ ($X^2\Pi$) radical) are short-lived paramagnetic particles. The late two – because of the odd number of electrons and one non-paired electron spin, the singlet $O_2(a^1\Delta_g)$ oxygen – because of the orbital magnetic moment [4].

Let me remind you that an electron is a tiny magnet; its magnetic moment (spin S = ½) has a pure quantum origin and no evident analogy in the visible macroscopic world. The electron spin arrow in contrast to classical magnet has only two possible orientations (M_s = ±½) determined by the pure quantum nature of such elementary particle [3]. Most free

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atoms (besides Nobel gases) have non-paired electrons. Being in chemical reactions and entering a molecule the atoms produce spin pairing which accompanies the chemical bond formation [3]. The dioxygen O = O molecule possesses a double chemical bond. However, because of the special orbital symmetry of the O_2 valence shell, its ground state with the lowest energy (the most stable state) keeps two non-paired electrons with the parallel spins orientation (↑↑). Such the ground O_2 state has a non-zero total electronic spin (S = ½+½ = 1) which can possess only three possible projections on the molecular axis (M_s = 0,±1); thus, this state is called a triplet. In contrast, the typical organic molecules with antiparallel spins (↑↓) have a total electronic spin S =0 [4] (no intrinsic magnetic moment), which corresponds to a singlet diamagnetic state. The first excited state of O_2 possesses also antiparallel spins; thus it is a singlet $O_2(a^1\Delta_g)$ oxygen [3]. This state is doubly degenerate; that is, there are two states with the same energy of 22 kcal/mole above the ground triplet state $O_2(X^3\Sigma_g)$ [5]. The degenerate character of the singlet $O_2(a^1\Delta_g)$ oxygen is very often ignored in many biomedical studies on Photodynamic Therapy (PDT) which hinders the proper understanding of real electronic mechanisms behind the PDT phenomena [5]. The degeneracy of the singlet $O_2(a^1\Delta_g)$ state determines its orbital magnetic moment providing a rather unusual paramagnetic character of this reactive oxygen species.

The spin importance in biology was discovered by Linus Poling in his studies of hemoglobin [2]. The Fe(II) ion in hemoglobin is spin paramagnetic and its coupling with O_2 is a complicated process depending on the spin state of dioxygen, on the exchange and spin-orbit coupling between heme and the air molecules [6,7]. This mini-review is devoted to describing spin-dependent essential features of dioxygen $O_2(X^3\Sigma_g)$ and $O_2(a^1\Delta_g)$ states superoxide $O_2^{\cdot-}$ ion, and other ROS involvements in interactions with human dermal papilla cells and melanocytes which are important players in hair pigmentation and hair growth, as well as response to physiological dioxygen level (5% O_2, hypoxia) on melanocytes proliferation, papilla cells migration and tyrosinase enzyme activity.

General data on dioxygen reactivity

Dioxygen reactivity strongly depends on a small number of possible activators or special enzymes. It is well known, that the triplet $O_2(X^3\Sigma_g)$ dioxygen from the air could be either chemically extremely active or completely inert depending on the presence of paramagnetic radicals in the nearest environment [1-10]. This transparent gas can show furious activity in combustion, for all that being billion years passive in the Earth's atmosphere [1,2]. Triplet dioxygen protects our life on the Earth's surface from dangerous solar Ultraviolet (UV) radiation through its absorption in the 175 nm - 205 nm region (the Schumann-Runge absorption band), creates a stratospheric ozone layer which protects us from the soft UV light (240 nm), and provides respiration energy of all aerobic life [6]. Since the majority of organic molecules (M) are diamagnetic species, their reactions with triplet $O_2(X^3\Sigma_g)$ dioxygen are completely spin-forbidden processes; the final Products (P) of such possible oxidation are also diamagnetic molecules (H_2O, N_2, and CO_2) [7]:

$$M\ (\uparrow\downarrow) + O_2\ (\uparrow\uparrow) \neq P\ (\uparrow\downarrow)\ (\uparrow\downarrow) \quad (1)$$

The spin-flip is obvious to complete such a reaction, Eq. (1). The flip of the spin magnetic moment in Eq. (1) can only be induced by magnetic interaction (with the external field or through internal perturbations) [6]. It is known, however, that external magnetic fields are not necessary for organic oxidation reactions to proceed [7]. The structure of chemical bonds and chemical reactions are determined mostly by internal electric forces (these are electrostatic interactions between the charged elemental micro-particles, electrons and nuclei) [1]. Pure magnetic intrinsic interactions are extremely weak in molecules consisting of light atoms; that is why magnetic intrinsic interactions are reasonably neglected in the Schrodinger equation of traditional quantum chemistry [7]. This is the reason why the reaction of Eq. (1) is considered to be forbidden by the Wigner-Witmer rule for spin conservation in chemical reactions [11]. The question about combustion and respiration is clearly solved only in the first case; the combustion mechanism, Eq. (1), proceeds through intermediate chain reactions being initiated by radicals (R), the reactive species with non-paired electrons, Eq. (2):

$$M\ (\uparrow\downarrow) + O_2\ (\uparrow\uparrow) + R\ (\downarrow) = P^{\cdot}\ (\uparrow\downarrow)\ (\uparrow\downarrow) + R^{\cdot}\ (\uparrow) \quad (2)$$

The newborn radical $R^{\cdot}$ and intermediate diamagnetic product $P^{\cdot}$ can continue the chain; $R^{\cdot}$ can react again with dioxygen without spin-prohibition. The total spin (S = 1/2) and its projection (M_s = +1/2) are the same in the right and left parts of Eq. (2). This is because the particular spin orientation upon O_2 (↑↑) and R (↓) collision is possible in Eq. (2) [7]. The next organic molecule M can react with O_2 and provide a diamagnetic product through the intermediate radical involvement. That is why the combustion proceeds as a radical chain reaction one of the chain links of which is presented by Eq. (2) [2,7].

It is well known that respiration and combustion are finally identical in the exothermic effects of reaction and in the full oxidation products (all organic fuels are completely oxidized to CO_2, H_2O and N_2) [2]. Because of such a final identity, a naïve question could occur: what is that bio activator that provides "a match" to initiate the first radical for the respiration chain in the cell? The answer is obvious; the respiration cannot proceed through the radical-chain reaction mechanism, since it is not compatible with the temperature of most mammalians; the radicals would burn the cell.

At the necessary high concentrations, free radicals are hazardous species for living cells; they can damage the major cellular constituents [1,2]. At a moderate concentration, however, superoxide anion-radical, like other Reactive Oxygen Species (ROS) can play a crucial role as a regulatory mediator in the cell signaling processes. The ROS-mediated responses can reestablish the "redox homeostasis" and protect the cell against oxidative stress [7-9]. Such ROS response can provide regulation of vascular tone, monitoring of O_2 tension in the control of erythropoietin (Epo) production in the kidney and in membrane receptors signal transduction in numerous physiological processes [1]. ROS and nitric oxide are usually generated in such cases by tightly regulated enzymes like

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NAD(P)H oxidase and nitric oxide synthase (NOS), respectively [12]. In mitochondria, ROS are generated by many enzymes as side products (most undesirable) of oxidative metabolism [10-21]. An excessive increase in ROS production is responsible for the pathogenesis of cancer, atherosclerosis, diabetes, neurodegenerative diseases, rheumatoid arthritis, ischemia and other diseases. Finally, paramagnetic free radicals are connected with the process of deterioration with age and senescence [2,12].

Most intracellular ROS are derived from superoxide anion-radical ($O_2^{-\bullet}$) being generated by one-electron reduction of dioxygen. The superoxide radical is transferred to hydrogen peroxide by superoxide dismutases (SODs) [12]. Singlet oxygen $O_2(a^1\Delta_g)$ generation in the dark cell typically occurs through the oxidation of superoxide $O_2^{-\bullet}$ anion [9]. Finally, the Fenton reaction can lead to the hydroxyl OH$\bullet$ radical, the most dangerous ROS agent [22]. Thus, the internal magnetic properties of superoxide play a fundamental role in ROS production and their functionality, though not many chemists [13] pay attention to the spin-orbit coupling mechanism [15] which affords $O_2^{-\bullet}$ anion to overcome spin prohibition for dioxygen activity.

The most fundamental processes of aerobic life are spin forbidden

The respiration mechanism is arranged as the Krebs cycle of tricarboxylic acid; this is a complicated multistep process where O_2 is activated by enzymes that contain paramagnetic metal ions [2,7]. The metal ions provide the non-zero spin of non-paired electrons which interact with the triplet spin of O_2 by exchange coupling; formally this is a spin-allowed process that is similar in a way to Eq. (2) [7]. However, there is a great difference, since the spin of metal ions is not a free radical being tightly bound with organic ligands of the enzyme [4-7]. The Fe(II) ion in hemoglobin is also paramagnetic and its coupling with O_2 and NO is a complicated process depending on the exchange and spin-orbit coupling [4-7]. Thus, two basic processes of all aerobic life, photosynthesis in chloroplasts and respiration in mitochondria

$$6H_2O + 6CO_2 + h\nu \xrightarrow{chlorophyll} C_6H_{12}O_6 + 6O_2$$

$$C_6H_{12}O_6 + 6O_2 \xrightarrow{enzymes} 6H_2O + 6CO_2 + energy \Leftrightarrow (ATP)$$

Represent spin-forbidden reactions activated by the presence of paramagnetic Mg (II) and Fe(II) ions in chlorophyll and in cytochrome *c* oxidase, respectively [5]. The triplet O_2 (↑↑) molecule from the air can penetrate through the lung alveolus and being bound by paramagnetic Fe(II) ions of hemoglobin is transported to a cell where it realizes great work in mitochondria [10,19]. Besides respiration O_2 molecule provides other numerous oxidation reactions being activated by various oxidases, mono- and di-oxygenases [13]. Many of these enzymes also contain paramagnetic metal cofactors, but many others include pure organic flavins and pterin cofactors without paramagnetic species [5,13]. Their mechanisms of O_2 activation which help to overcome the dioxygen spin prohibition [15] are still not known among the modern biomedical community [1,2,13,18]. Meanwhile, the well-grounded physical concept of strong internal magnetic perturbation inside the intermediate superoxide (spin-orbit coupling in $O_2^{-\bullet}$ anion-radical) [15] can explain all kinetic peculiarities of metal-free oxidative enzymes [5]. Moreover, nowadays there are discovered several new enzymes which do not possess cofactor at all; however, they can activate dioxygen for substrate oxidation providing a great puzzle in modern biochemistry [13,20]. The theory of spin-orbit coupling in $O_2^{-\bullet}$ anion naturally explains the mechanism even for these cofactor-free oxidases and oxygenases [16]. Though, few practical biochemists [20] have already accepted and utilized the idea of strong magnetic torque in superoxide radical [5,17] a large biochemical community is not informed so far [13] about the spin-orbit coupling theory of the superoxide ion as the main factor of aerobic metabolism. Implications of this knowledge in biomedical practice should be useful for the treatment of many diseases including dermatology where dioxygen is one of the important players [12,18-25].

Thus, dioxygen is vital for living cells and plays a fundamental role in cellular metabolism. However, the simple molecular diffusion of O_2 gas in tissues is not sufficient for an understanding of the metabolic needs of large, active, and complex multicellular organisms when dioxygen reactivity with organic stuff is forbidden by severe quantum rule for spin selection. Consequently, it is necessary to provide tissues and cells with numerous activators of dioxygen which can help them to overcome spin prohibition without the assistance of paramagnetic metals [5,7].

How oxidative enzymes can overcome spin prohibition for O_2 activation

Numerous enzymes of pure organic nature can really activate dioxygen without vital metal assistance [5]. Flavin- and pterin-dependent oxidative enzymes are ubiquitous in living organisms [13]. Their hetero-aromatic cycles can undergo multistep electron transfer demonstrating reach redox chemistry [13-16]. Various redox phases of flavins and pterin play important roles in electron-coupled proton transfer processes which are crucial for many important biochemical functions, such as biosynthesis, oxidation, DNA repair, detoxification and biodegradation [12,21-29]. During reactions catalyzed by flavin - and pterin-dependent enzymes numerous forms of transient Radical Pair (RP) can be generated, including FADH$\bullet$...$O_2^{-\bullet}$ radical pair [13].

Flavoenzymes oxidation is studied in many details [13]. The reduced flavin (Fl^{red}) is usually oxidized to semiquinone ($Fl^{sq\bullet}$) radical during interaction with O_2 and followed by flavoperoxide FlOOH subsequent formation [5]. Vincent Massey has postulated an electron transfer from the reduced flavin to dioxygen with the intermediate triplet RP formation between $O_2^{-\cdot}$ ion and semiquinone $Fl^{sq\bullet}$ radical in the following form [14]:

$$Fl^{red}(\downarrow\uparrow) + O_2(\uparrow)(\uparrow) \rightarrow [Fl^{sq\bullet}\uparrow\uparrow O_2^{-\cdot}] \rightarrow [Fl^{sq\bullet}\uparrow\downarrow O_2^{-\cdot}] \rightarrow FlOO^{-} \rightarrow FlOOH \quad (3)$$

In Eq. (3) the spin-flip occurs at the triplet ↑↑ RP stage, which needs to undergo the triplet-singlet transition in order

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to form a diamagnetic FlOO- adduct. As an example, glucose oxidase (GO) can be considered [15]. A reduced deprotonated flavin in the form of the $FADH^-$ anion at the beginning of oxidative half-reactions of glucose oxidase can produce an electron transfer to the triplet O_2 molecule and form the triplet radical pair between semiquinone $Fl^{sq\cdot}$ (↑) and superoxide $O_2^{-\cdot}$ (↑) radicals, Eq. (3). This triplet RP has to undergo spin-flip in order to continue the usual singlet-state chemistry [15]. Vincent Massey had not commented on the magnetic origin of those forces which are responsible for the spin-transition in Eq. (3) [7,16]. But one can suspect that he had taken in mind the Radical Pair Theory (RPT) [15,27,28], which was rather popular twenty years ago for the Magnetic Field Effects (MFE) explanations in chemical reactions. The RPT considers the possibility of the Triplet-Singlet (T-S) transition [28] in radical reactions which are induced by Hyperfine Interaction (HFI) between electron and nuclear spins. This is possible only in the separated radicals being inside a non-bound RP [28]. The T and S states of such RP are degenerate (possess the same energy) according to RPT; that is why even a weak HFI can produce the T-S transition [28]. The RPT could be applied to free flavins in aqua solvent but it cannot be applicable to a real enzyme, where FADH and $O_2^{-\cdot}$ are kept tightly bound like in the GO active site [7,21]. The driving force origin of the spin transition in Eq. (3) is the main problem of O_2 activation by numerous free-of-metal enzymes [7]. To unravel the knowledge of the such mechanism is important for many practical biomedical applications [12-29] (like photodynamic therapy and psoriasis treatment). Extremely weak hyperfine interactions cannot induce a competitively fast triplet-singlet transition in radical pair Eq. (3) of the enzyme active center [19]. The rate constant of the T-S spin-flip has to compete with the dissociation of the RP triplet state in Eq. (3). Such RP dissociation would lead to the dangerous and active superoxide-ion release into the cytoplasm. Thus, understanding the origin of the driving force for the T-S spin-flip in Eq. (3) is so important for the medical treatment of many diseases including skin disorders.

The first explanation of the T-S inter-conversion in Eq. (3) has been proposed twenty years ago [15] and based on account of two electronic configurations being possible in the degenerate open shell $(\pi_g)^3$ of the superoxide ion-radical, (↑)(↓↑) and (↓↑)(↓); here the brackets denote the $\pi_{g,x}$ and $\pi_{g,y}$ molecular orbitals of O_2 [15]. Therefore, the T-S transition in the radical pair, Eq. (3), can be presented as

$$^3[Fl^{sq\cdot}(\uparrow)...(\uparrow)(\downarrow\uparrow)O_2^{-\cdot}] \rightarrow {}^1[Fl^{sq\cdot}(\uparrow)...(\downarrow\uparrow)(\downarrow)O_2^{-\cdot}] \quad (4)$$

The arrow in Eq. (4) denotes Spin-Orbit Coupling (SOC) as a driving force of the spin-flip [5]. The left upper symbols in Eq. (4) mean the triplet and singlet states; they differ by electronic configurations inside the superoxide ion whereas the spin of flavin semiquinone radical is the same in the left and right. The T-S transition in Eq. (4) corresponds to orbital rotation $\pi_{g,x} \rightarrow \pi_{g,y}$ for one electron with its simultaneous spin flip inside superoxide $O_2^{-\cdot}$. Such orbital rotation can create a magnetic torque responsible for the spin T-S inter-conversion [7,19]. The triplet and singlet states in Eq. (4) according to quantum perturbation theory are connected by the strong SOC which is equal to ½ A_{so}, where A_{so} is a SOC constant of the ground state $X^2\Pi$ of the diatomic radical (or $O_2^{-\cdot}$ molecule) [5,15]. According to simple approximation [19], the $A_{so}(X^2\Pi, O_2^{-\cdot})$ constant coincides with the SOC-induced splitting of the ground state of the oxygen atom A_{so} $O(^3P) = \zeta_O$ being close to a value 160 cm^{-1} [5,7]. Such a simple analysis is supported by experimental measurement of the $O_2^{-\cdot}$ ion fine structure [30]. This energy is much larger than the hyperfine nuclear-electron spins interaction in the radical pair theory [27-29]. It is relevant now in connection with dermatology to consider photodynamic therapy (PDT) and external magnetic field effects (MFE) in biology and medicine [5,10,27-29].

The role of spin-orbit coupling in biology and medicine

Weak magnetic fields and MFE applications are very popular in modern biochemistry and biomedicine [27-29]. Sensitivity to weak MFE has been studied in the bird's magnetoreception [29], circadian clock, brain activity, memory, anxiety, genetics and many other biological phenomena [28]. The main achievements in the MFE understanding are connected with the RPT application to electron transfer in cryptochrome and in neuronal activities [28,29].

The RPT mechanisms were successfully applied to cryptochrome in the bird's magnetoreception and navigation in the weak magnetic field of the Earth during the long intercontinental bird flights [27,28]. This RPT considers radical pairs which can possess either singlet or triplet spin state. In the S state, two radicals can recombine; however, they can only scatter in the T state since the parallel spin orientation does not lead to covalent bonding [29]. When the triplet RP collides in a solvent, the radicals go apart and there is a possibility for the T-S transition during the radicals diffusion in the solvent cage. The rate of such spin-flip depends on HFI and the external magnetic field [28]. The newborn singlet radical pair can recombine in the secondary collision [28]. Since the spin interaction with a weak magnetic field of a few millitesla (mT) is much smaller than thermal energy, only RPT can explain such MFE observation.

Zheng, et al. have applied the RPT ideas and shown that a static magnetic field of 4 mT can regulate the migration, proliferation and differentiation of human dental pulp stem cells [31]. Exposure of human monocytic U937 cells to the external magnetic field of 6 mT was shown to decrease macrophagic differentiation [28]. The renal cell cultures and cortical astrocytes were influenced by weak MFE in the field of 0.6 mT which can also induce for patients with Parkinson's disease the dopamine-dependent change in cortical excitability [28]. All these MFEs are supposed to be explained with the RPT; however, the biomedical mechanisms are far from detailed explanations [28]. It was shown that oxygen gas is necessary for the detection of spin changes in the course of xenon-induced anesthesia; accounting for these observations, the authors [28] proposed that an electron transfer will play a crucial role in the recombination of RP between tryptophan cation-radical and superoxide anion in the xenon's anesthetic action. From our point of view, the involvement of $O_2^{-\cdot}$ anion will definitely lead to the SOC-induced mechanism (the Eq. (3) type) in such

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RP recombination. The T-S transition process will be driven by strong SOC in superoxide, not by RP theory.

One should also mention that numerous MFE fixations studied so far are poorly reproduced and the RTP interpretations of magnetic field influence on dioxygen functionality [19,28] are rather suspicious. One should stress that the most solid inference with respect to the internal magnetic interaction influence on dioxygen reactivity in living aerobic cells is connected with Eq. (4) and the role of SOC in oxygenation enzymes [17].

Spin effects in reactive oxygen species and oxidative stress in dermatology

Skin is the largest organ of our body; it serves as a protective barrier being our frontier line of defense from reactive chemicals, UV solar light and other hazards. The singlet excited oxygen $O_2(a^1\Delta_g)$ and superoxide $O_2^{-\cdot}(X^2\Pi_g)$ radicals are the most important reactive oxygen species (ROS) [18,32]. Excessive generation of ROS and oxidative stress play a crucial role in the pathogenesis of many diseases [1,26,33]. Respiration produces ATP molecules through oxidative phosphorylation, along with O_2 and glucose consumption in mitochondria. Defects of mitochondria lead to numerous predictable dysfunctions in most tissues [24,33].

Superoxide $O_2^{-\cdot}$ ion-radical can escape from oxidative enzymes and destroy mitochondria if the T-S spin-flip in Eq. (4) is not fast enough in order to compete with the dissociation of the radical pair described by Eq. (3). The rate of the spin-flip can deviate from the normal working regime since it strongly depends on the hindered rotation of the $O_2^{-\cdot}$ radical in the enzyme active center and on the low-frequency vibration in the nearest protein environment [16,28].

A small diatomic O_2 molecule can easily penetrate through the cell membrane; hence, the decreased concentration of dissolved O_2 around the cell (in the cellular milieu) can be used to determine dioxygen consumption by the target cell [32]. Electrochemical microelectrodes can provide accurate measurements of dissolved oxygen by microfluidic chips. Optical sensors using dye fluorescence and phosphorescence can be also useful to monitor dioxygen concentration [32,33]. The singlet oxygen $O_2(a^1\Delta_g)$ is usually detected in tissue through its extremely weak near-IR luminescence (1.27 μm) in the singlet-triplet transition $O_2(a^1\Delta_g) \rightarrow O_2(X^3\Sigma_g)$ which is doubly prohibited by orbital selection rules being also spin-forbidden [5]. Quantum-chemical calculations of the dioxygen S and T states wave functions in the electronic open shell $O_2(\pi_g)^2$ and its spectral analysis provide a new look at the role of intrinsic magnetic interactions, which make it possible to overcome orbital and spin prohibitions in such fundamental phenomena like biological oxidation and light emission by dioxygen [7,34]. The first derivation of Eq. (4) was proposed during the spectroscopy problems study [35] connected with the singlet oxygen $O_2(a^1\Delta_g)$ quenching in the gas phase by amines. The way from optical spectra to enzymology takes more than twenty years [10,35].

The geological history of aerobic evolution recorded by numerous fingerprints on the mountain rocks indicates the ROS occurrence since the very beginning of the photosynthetic era; it shows the primordial importance and "strategic" role of spin prohibition for the triplet $O_2(X^3\Sigma_g)$ dioxygen reactions with organic matter and with sunlight [19,36]. The triplet nature of $O_2(X^3\Sigma_g)$ molecule and spin restrictions clearly explains why our world had not been burnt in a fire during the Great Oxygenation Catastrophe (GOC) two billion years ago [12,36] when the photosynthetic bacteria and green-blue algae had started to fulfill the Earth's atmosphere by dioxygen molecules. Anaerobic bacteria and archaea had perished during GOC and been substituted by eukaryotes; the more efficient type of life evolution had followed by [2,36]. The primordial atmosphere before GOC did not contain O_2; with dioxygen occurring the new organelles - mitochondria - were evolved which provided oxidative phosphorylation and electrochemical proton gradient across membranes for the electron transport chain [36]. The role of mitochondria is known to extend far beyond the glucose oxidation-phosphorylation in living cells. Mitochondria's new role discovered recently [12] concerns their involvement in ion homeostasis and apoptosis through the signaling functions of ROS. It was proposed that ROS occurred on the Earth's planet simultaneously with photosynthetic dioxygen [12]. The high level of ferrous Fe(II) cations in the primordial ocean could lead to dioxygen reduction and superoxide generation. The $O_2^{-\cdot}$ radical could dismutate to form H_2O_2; then, the hydrogen peroxide interacting with the soluble Fe(II) cations by the Fenton reaction [22,37] could produce highly reactive hydroxyl $OH^{\cdot}$ radical [12]. All these simple molecules, together with the singlet oxygen $O_2(a^1\Delta_g)$ produced by natural dyes in solar light, constitute the known ROS. Thus, the reactive oxygen species had occurred in a natural manner at the very GOC beginning. Latter on ROS plaid an important role in the long aerobic life evolution. One should note that superoxide dismutase (SOD) as the oldest enzyme on the Earth was developed to scavenge all ROS very effectively. The SOD was found in all kingdoms of life [12] and evolved in GOC time even earlier than archaea-eukaryotes differentiation happened [36]. The Great Oxygen Catastrophe was the first ecological disaster that shacked the Earth; it lefts many records that show clearly the SOD history in the early Earth's time. The role of paramagnetic spin factors in the ROS and SOD activity including the importance of spin-orbit coupling effects are described in several recent reviews [7,19,27,34,38].

Dioxygen and ROS in skin problems

We know that ROS are generated by peroxisomes and by mitochondria during normal cellular metabolism [18]. ROS generation may be increased under some pathologic conditions, like inflammation and cancer, upon exposure to various exogenous factors (UV light, chemicals, etc.) [23]. The skin forms a large part of our body which interfaces with the milieu environment; moreover, it is the largest source of reactive oxygen species that are induced by solar light exposure. The epidermal melanocytes are especially at risk and vulnerable to redundant ROS generation due to their particular function: melanin synthesis that is stimulated by sunlight exposure,

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during tanning, and by inflammation which results in hyperpigmentation [23]. Oxidative stress (OS) can result from the excessive over-production of ROS in the cell and from a decrease of antioxidant cellular capacity; OS can damage lipids, proteins and DNA leading to lipids peroxidation, mutagenesis or even to cell death [18].

The epidermal melanocytes usually play the main role in the skin's response to sunlight exposure. They are primarily involved in light-induced pigmentation being the first defense mechanism. The melanocyte's alternation, however, can lead to melanoma. The role of singlet oxygen $O_2(a^1\Delta_g)$ in such a transformation process whereby UV-light damage could result in melanoma initiation so far is poorly understood. One should remember that in pigmented cells melanin can work either as a light screen or as the $O_2(a^1\Delta_g)$ photosensitizer, which is important for UV-induced genotoxicity [18,24]. The homeostasis of epidermal melanocytes in human skin is maintained by a paracrine network primarily consisting of growth factors as well as cytokines synthesized by dermal fibroblasts and by epidermal keratinocytes, all being modulated by UV radiation [23]. Little is known about the mechanisms and energetics of hair follicles growing, especially in the bulb abundant by mitochondria [39]. Nowadays, mitochondrial and oxidative metabolism can be visualized by multiphoton microscopy in plucked human hairs and in cultured bovine hair follicles [25,39].

Extensive ROS-induced oxidative stress can play a main role in the aging process. ROS are typically generated by numerous endogenous and environmental challenges. Our body and skin possess some endogenous defense mechanisms, like antioxidative enzymes and simple antioxidant molecules, protecting us from ROS free radicals by scavenging, reducing, and neutralizing them. The production of free radicals increases with age, while the endogenous protection mechanisms decrease. Such misbalance leads to progressive damage of many cellular structures, resulting (presumably) in the aging phenotype. Hair aging is known to manifest itself as a melanocyte function decrease or graying, as well as a reduction in hair growth and hair loss (alopecia) [37]. There is evidence that OS may be responsible for the mechanism which contributes to hair graying. Nowadays we know the SOC effect and electron transfer can influence quantum transitions between different forms of dioxygen ROS radicals and birdcalls: $O_2(X^3\Sigma_g) \rightarrow O_2(a^1\Delta_g) \rightarrow O_2^{\cdot-}(X^2\Pi_g) \rightarrow OH^{\cdot}(X^2\Pi_{1/2})$ [5,19]. New insights into the role of spin-dependent effects and paramagnetic properties of dioxygen and ROS could help to prevent oxidative stress and open new strategies for the reversal of the hair-graying process and age-dependent alopecia [37]. New perspective treatments of skin diseases are associated with androgen receptors, inflammation, and oxidative stress therapeutics [37,40]. Androgens are natural male sex hormone and their interaction with receptors strongly depends on low-frequency vibrations energy transfer [26,41]. The similar vibronic relaxation accompanies the T-S spin transitions in $Fl...O_2^{\cdot-}$ radical pairs, Eq. (4) and in the singlet oxygen $O_2(a^1\Delta_g)$ quenching process [35,41,42]. Quantum-chemical calculations of electron-vibration (vibronic) coupling in androgen receptors [26,41] show that spin-dependent ROS activity can influence skin biology in a very peculiar mechanism.

Skin is always under oxidative stress impacted by the environment. The Nrf2 (nuclear factor erythroid 2–related factor 2) as a regulator of cell resistance to oxidants is of crucial importance for skin [9]. The Nrf2 is a master transcription factor to regulate cellular redox and oxidative stress in skin diseases [37]. Sex hormones are important not only in regulating the reproductive systems but also in skin functions. Steroid hormone receptors (for testosterone, estradiol and estriol) are expressed in numerous types of skin cells, such as epithelia of sebaceous glands, dermal papillae, and fibroblasts [26,37,41]. Some skin diseases are androgen-dependent being associated with a dysfunction of androgen receptors signaling systems, such as androgenetic alopecia, hirsutism, acne vulgaris, and hidradenitis suppurativa [37]. Microscopic connections between ROS and androgen receptor signaling systems are not fully understood but their study seems to be useful for dermatology.

Conclusion

Promoting efficient therapeutics for skin diseases represents a big challenge in modern biomedicine since the pathogenesis of skin disorders is rather complicated and is dependent on many factors including ROS and UV causes. The spin-dependent effects and paramagnetic properties of various ROS are considered in this review in the general context of dioxygen reactivity and dermatology.

Aerobic respiration and photosynthesis are totally spin-forbidden multistep processes that are activated by the presence of paramagnetic metal ions and their exchange perturbations. At all this, numerous metabolic oxygenation processes are catalyzed by the free-of-metal enzymes. They act by an electron transfer step from organic substrate or cofactor (M) to dioxygen and ion $O_2^{\cdot-}$ generation. The T-S spin-flip occurs at this RP step $M^{+\cdot}...O_2^{\cdot-}$ being induced by spin-orbit coupling inside the superoxide anion. Similar RP steps may operate in epidermal melanocytes of the skin. One should realize at the same time, that this mechanism differs from the known radical pair theory which is often applied to explain magnetic-field therapy.

The new SOC mechanism, Eq. (4), is widely spread in redox O_2 biochemistry, being the only way to activate the T-S spin flip in dioxygen without external paramagnetic assistance. It can explain O_2 activation by numerous flavor enzymes, as well as cofactor-free dioxygenase. Magnetic torque in the superoxide open shell is one of the main driving forces for ROS production and O_2 activation in many oxidative enzymes. The triplet O_2 molecule exercises sluggish chemical reactivity in the absence of paramagnetic organic radicals or metal ions. In living matter (especially in skin) dioxygen shows very efficient activity because of the intermediate action of superoxide and other ROS. Future medicine will pay more attention to the spin effects of dioxygen.

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