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Vitiligo and Hashimoto's thyroiditis: Autoimmune diseases linked by clinical presentation, biochemical commonality, and autoimmune/oxidative stress-mediated toxicity pathogenesis

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ABSTRACT

Vitiligo (VL) is a chronic autoimmune pigmentation disorder characterized by destruction of melanocytes. The condition is associated with several other autoimmune diseases, but autoimmune thyroid diseases, especially Hashimoto's thyroiditis (HT), is the most prevalent organ-specific autoimmune disease with a co-morbidity up to 34%. Among the many hypotheses that have been proposed for the pathogenesis of both diseases, autoimmunity and oxidative stress-mediated toxicity in melanocytes or thyrocytes, respectively, have been the most widely accepted – with autoimmunity being the presumed consequence of oxidative stress-mediated toxicity. However, the predominant etiologic basis for impairment of redox balance has rarely been studied. The two autoimmune diseases are not only linked by a concordance of clinical presentations and an autoimmune/oxidative stress-mediated toxicity pathogenesis but also by an apparent biochemical commonality. The target molecules produced in the thyroid and skin, i.e., thyroxine and melanin, respectively, are derived from the same primordial parent molecule, tyrosine. On the basis of these similarities between Hashimoto's thyroiditis and vitiligo, specifically with respect to the activation of oxidative stress, we propose a novel hypothesis accounting for the destruction of melanocytes or thyrocytes in VL and AT. We suggest a new therapeutic regimen of quinone derivatives to combat ROS-induced autoimmunity resulting from this common biochemical etiologic error.

Introduction

Vitiligo (VL) is a cutaneous autoimmune disease of pigmentation characterized by the development of well-defined white patches on the skin and mucous membranes. It is a relatively common condition with a prevalence of 0.5–1% in the world population [1,2]. The disease is especially devastating to patients with darker skin tones, which can have a profound impact on the quality of life of both children and adults afflicted with the disorder. Patients with vitiligo often experience stigmatization, social isolation and low self-esteem [3,4]. It is widely known that vitiligo is associated with several autoimmune diseases, but autoimmune thyroid diseases, especially Hashimoto's thyroiditis (HT), predominantly seen in women, is the most prevalent organ-specific autoimmune disease [5] with a comorbidity of up to 34% in vitiligo patients [6–8]. The pathological distinction for the two diseases is between a loss (or diminution) of epidermal melanocytes or of thyrocytes.

Despite a wealth of scientific publications, pathogenic mechanisms underlying VL and HT remain unknown. Among the various hypotheses that have been proposed for the pathogenesis of these diseases, autoimmunity and oxidative stress-mediated toxicity in melanocytes and thyrocytes have been the most widely accepted. The autoimmune hypothesis won its popularity by the finding of serum autoantibodies which reacted with and destroyed melanocytes and thyroid components such as thyroglobulin (Tg) and thyroperoxidase (TPO) [9]. The high degree of familial aggregation without any obvious Mendelian pattern of inheritance suggests that a large number of etiologic factors in nature may be involved in both diseases. The clinical association of VL with autoimmune thyroid disease, moreover, indicates the possible presence of shared heritable susceptibility genes. Furthermore, the two autoimmune diseases are not only linked by an autoimmune/oxidative stress-mediated toxicity pathogenesis but also by a similarity of clinical presentation and biochemical commonality. At the biochemical level, the similarity between the two disorders also extends to the target molecules produced in the thyroid and skin, i.e., thyroxine and

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melanin, respectively, both of which are derived from the same primordial parent molecule tyrosine. On the basis of these similarities between Hashimoto's thyroiditis and vitiligo phenotypes, specifically with respect to the activation of oxidative stress, and premature senescence, it is very likely that autophagy-deficient thyrocytes and vitiligo melanocytes share defective cellular redox regulation, increased membrane lipid oxidation, and premature senescence.

The hypothesis/theory

Taken together, the similarities of vitiligo and Hashimoto's thyroiditis: linked by clinical presentation, biochemical commonality, and an autoimmune pathogenesis, provide a basis for a unifying hypothesis to explore new ideas for the pathogenesis of the two disorders that could lead to new diagnostic and therapeutic applications. The hypothesis is different from current thinking since it utilizes a technique for prediction of an outcome in situations where there are limited data but where areas of similarity exist. The hypothesis utilizes the stochastic method developed by Pauling for his prediction of crystalline structure and composition of molecular structures and was used successfully in his discovery of the α-helix and pleated sheets in proteins and of the DNA double helix [10]. The word stochastic is derived from the Greek word, στοχαστική (stochastikí) meaning *apt to divine the truth by conjecture*. The method was especially valuable for Pauling when the data were not extensive enough to permit a straightforward derivation of structure based upon the use of all available information about bond lengths, valence, coordination, and polyhedral and other structural features needed to predict a likely crystalline structure, which then could be tested by comparison between calculated and observed diffraction patterns.

We hypothesize that the involvement of the thyroid and the skin is not due to mere happenstance but rather arises from a commonality in biochemical structure of the target molecules found in each organ. Thyroxine and melanin are both derived from the same primordial parent molecule tyrosine (Fig. 1). Because of the similarity between Hashimoto's thyroiditis and vitiligo phenotypes, specifically with respect to the activation of oxidative stress, and also with respect to premature senescence, we predict that autophagy-deficient thyrocytes and vitiligo melanocytes also share defective cellular redox regulation, increased membrane lipid oxidation, and premature senescence. Tyrosine oxidation produces melanin, while peroxidation produces thyroid hormones T3 and T4. Furthermore, both reactions are associated with superoxide formation that is coupled with the quinone cycling pathway that includes quinone (Q), semi-quinone (SQ^-) and quinol or hydroquinone (QH_2) involvement (Fig. 2). We hypothesize that the interruption of quinone metabolism in melanocytes and thyrocytes is the direct cause of the reduced production of melanin and thyroid hormones and is also the direct cause of an increase in superoxide radicals (including semi-quinone) which in turn triggers the oxidative stress-induced autoimmune response. By identifying the errant quinone targets in this pathway, we propose a means to test this hypothesis by use of a therapeutic regimen that includes quinone derivatives combined with supplements.

The scientific logic of the hypothesis is derived from the biochemical commonality between the synthesis of melanin and thyroid hormones; the causal assumptions are based upon the following:

Melanocytes and thyrocytes live under high oxidative pressures

From the standpoint of biosynthetic processes, melanin and thyroid hormones are oxidative products that are synthesized by a series of oxygenation and peroxidation reactions in melanocytes and thyrocytes, respectively. Because of this high oxygenation requirement, both types of cells are more vulnerable to any genetic modification in pathways responsible for ROS scavenging. Furthermore, pathways for synthesis of melanin and thyroxine start from tyrosine that can easily be converted to a tyrosine radical by light-induced oxidation in reaction with riboflavin (similar to the formation of semi-quinone from quinol by donation of a single electron) [11]. The second common chemical reaction between the two synthetic pathways is H_2O_2 formation. As shown in Fig. 1, generation of hydrogen peroxide is a normal by-product of eumelanin synthesis but is also a required component for thyroid hormone (T3/T4) synthesis. We predict that when the accumulation of superoxide quinone species exceeds some supposed limit to its normal redox capacity, the oxidative stress in melanocytes and thyrocytes initiates dilation of the endoplasmic reticulum (ER) (an observed histologic characteristic of melanocytes at the periphery of vitiligo lesions [12]. The accumulation of misfolded peptides leads to the activation of the unfolded protein response (UPR) [13]. Eventually, we predict that an apoptotic cascade occurs that then promotes the autoimmune response.

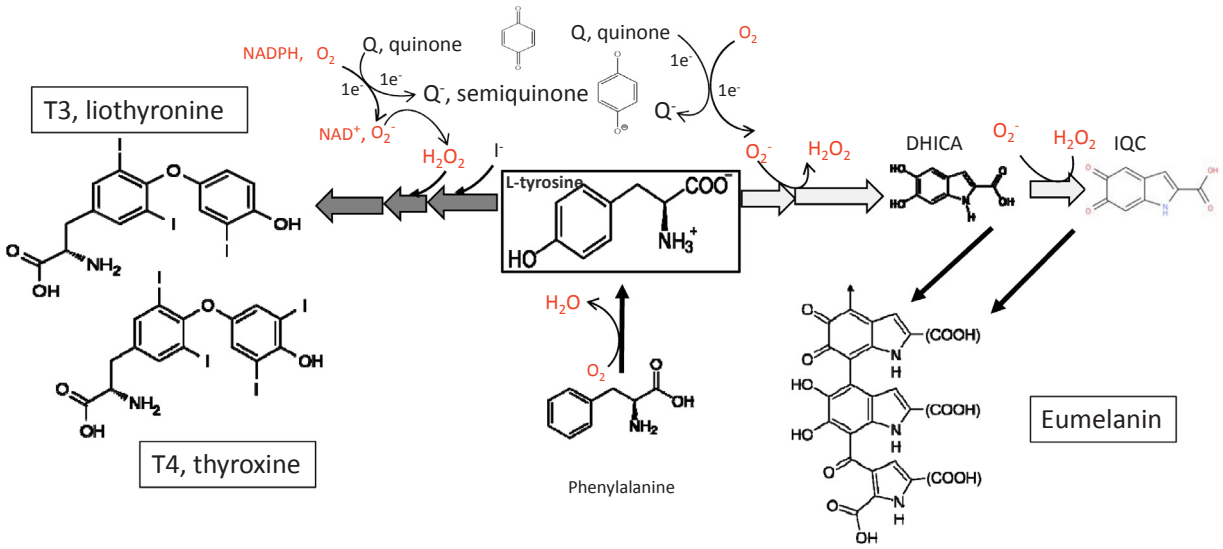

Fig. 1. Tyrosine oxidation (right) and peroxidation (left) are shown for eumelanin and thyroid hormone T3 and T4 synthesis, respectively. Both reactions are associated with superoxide formation that is coupled with quinone cycling from quinone (Q), semiquinone (SQ-) and hydroquinone (QH2). Any intrinsic defect in conversion of SQ- (superoxidized quinone) plays an early trigger to induce ROS- dependent apoptosis.

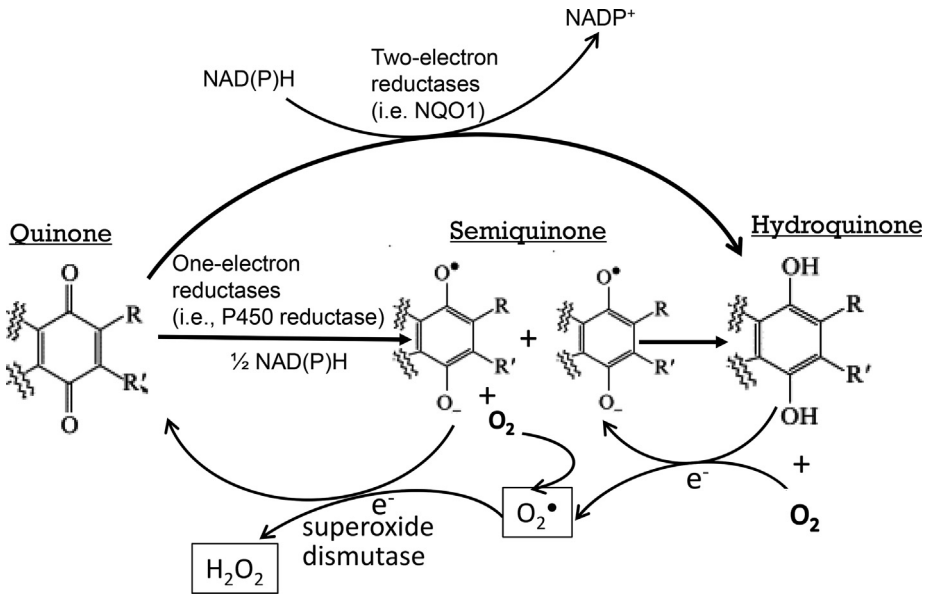

Fig. 2. Schematic representation of redox reactions occurring in Quinone cycling. Quinone is involved in three quinone types: quinone (Q, oxidized), semiquionone (SQ-) and hydroquinone (QH2). Quinone recycling also results in generation of H_2O_2.

The generation of hydrogen peroxide is coupled with quinone cycling

Quinone species are important cofactors that conduct electron transfer during the redox reaction in host cells. Typically, the oxidized quinones are converted into their corresponding reduced forms as hydroquinones after accepting two electrons. However, at times an oxidized quinone receives one electron or a quinol donates one electron that converts quinone or hydroquinone into semi-quinone. The latter reaction is also exactly the mechanism for hydrogen peroxide formation during thyroxine and eumelanin syntheses. In thyrocytes and melanocytes, L-hydroquinone is oxidized into a semi-quinone radical in order to provide a required electron transfer to an oxygen molecule moiety to form H_2O_2. This semi-quinone is chemically a very reactive superoxide that can be further oxidized into quinone in the presence of a suitable superoxide species such as O_2^- or the second O_2 may be converted into O_2^-. The superoxide dismutase then converts O_2^- into H_2O_2. In addition, two molecules of semi-quinone might undergo dismutation, leading to the production of one molecule of dopaquinone (Q type) and one molecule of L-dopa (QH_2) according to Vavricka et al. [14]. Therefore, SQ^- is the central molecule in quinone cycling during H_2O_2 formation (Fig. 2). We predict that whichever moiety SQ^- binds to, any errors in cycling SQ^- back to HQ or Q would increase the superoxide content, which would then trigger the downstream apoptotic cascades. We predict that the errors in VL and HT patients, as described below, involve several steps of Q cycling including electron transport chain (ETC) that would have pathologic consequences.

In mammalian cells, several intracellular flavoenzymes including NADPH-cytochrome P450 reductase and NADH-cytochrome b_5 reductase, mediate the one-electron reduction of quinones. Therefore, when two-electron quinone reductases reduce a wide spectrum of quinones, they compete with the one-electron reductases for access to the common quinone substrate. Because QH_2 is usually less reactive than SQ^-, any insufficiency of two-electron species would generally increase reactive oxygen species (ROS) production in quinone-exposed cells by favoring one-electron reductase-mediated redox cycling [15]. Ubiquinone (Co-enzyme Q) is the only lipid component of the mitochondrial ETC that shuttles back and forth laterally in the middle of the phospholipid bilayer. Quinone cycling occurs between complex I and complex III in the mitochondrial ETC as shown in Fig. 3. With electron transfer occurring among ETC complexes, ubiquinone (CoQ) is reduced to ubiquinol ($CoQH_2$) from NADH (CI) or $FADH_2$ (CII) dehydrogenations. Two molecules of the reduced form of $CoQH_2$ undergo a two-step Q cycling within CIII to convert into CoQ and $CoQH_2$ via the partially-reduced free radical form ($CoSQ^-$). As described above, the spontaneous combination of oxygen with $CoSQ^-$ is the major source of superoxide production within CIII [16]. The reduced form of CoQ_{10} ($CoQ_{10}H_2$) is the only known lipophilic antioxidant that human cells can synthesize *de novo* from CoQ_{10} via an enzymatic NAD(P)H-dependent mechanism. The $CoQ_{10}H_2$ can neutralize a lipid peroxyl radical by donating one of its hydrogen atoms to become $CoSQ^-$, which is then restored to a non-free radical state by the Q cycle. Therefore, the reduced form $CoQ_{10}H_2$ can serve as a potential therapeutic agent to prevent both the initiation and the propagation of lipoperoxidation in biological membranes [17].

The involvement of hydrogen peroxide generation in thyroid hormone synthesis

Shown in Fig. 4 are the redox reactions involved in the synthesis of thyroid hormones, illustrating in particular the role of H_2O_2 in these reactions. One-electron NAD(P)H reductase (e.g., P450 reductase) uses the SQ^- for hydrogen peroxide generation. Triiodothyronine (T3) and thyroxine (T4) are tyrosine-based hormones which are synthesized in thyrocytes in three steps: hydrogen peroxide generation, iodination, and coupling of one modified tyrosine with another. In the colloid, thyroid peroxidase oxidizes iodide (I^-) to iodine (I^0) which by its very electronegativity iodinates the thyroglobulin at tyrosyl residues in its protein chain (approximately 120 tyrosyl residues in total) in the presence of H_2O_2. The coupling of monoiodotyrosine (MIT) and/or diiodotyrosine (DIT) leads to the formation of T4 (two DITs paired together) or liothyronine T3 (one DIT and one MIT).

Quinone cycling involves two diphenol oxidation events in eumelanin synthesis

The end-products of melanogenesis are composed of a variety of monomers of quinone- and hydroquinone-related compounds, such as indolecarboxyl-quinone (ICAQ) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) as shown in Fig. 5. Alternatively, these two compounds can cross-link in the human melanocyte to complete the last step of melanin synthesis. The first event in whch Q- SQ^--QH_2-cycling is coupled to form *o*-dopaquinone-H^+ from L-dopa [17], the dopaquinone

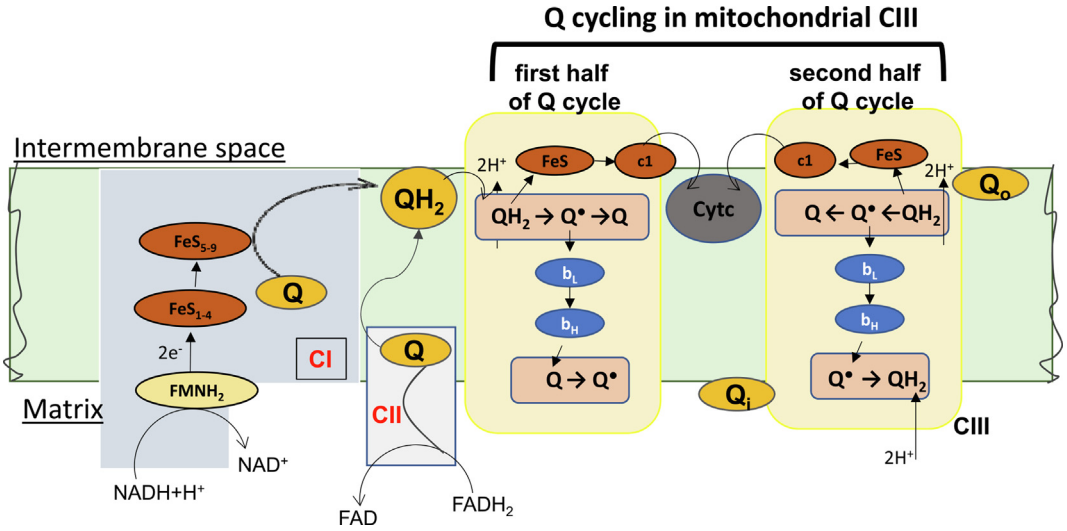

Fig. 3. Q cycling in mitochondria between complexes I or II and CIII. Through CI or CII, Q reduces to QH2, which is utilized by complex III. The electrons are then passed to cytochrome *c* (cytc) via two Q cycles. Abbreviations: FMN—flavin mononucleotide; Q—ubiquinone; Q˙—ubisemiquinone; QH_2—ubiquinol; Q_o and Q_i—the outer and inner sites of the Q-cycle, respectively; Fe-S—iron-sulfur clusters; bx and c1—b-type and c1 type hemes.

is then converted to dopachrome via an intramolecular cyclization. The second event takes place during the conversion of DHICA (phenol type) to ICAQ (quinone type of DHICA) [18]. According to Vavricka et al. [14], the DHICA-mediated pathway from dopachrome is more predominant in mammals, while the DHI-mediated pathway occurs more commonly in non-mammalian species. This second diphenol oxidation event in melanogenesis coupled with quinone cycling is different from the DHI to indolequinone (IQ) conversion in non-mammal melanization via a spontaneous decarboxylation step. One of the advantages of using melanogenesis instead of melanization is that DHICA is less vulnerable to non-enzymatic oxidation by ROS than is the melanization pathway, even though it rapidly forms the melanin polymers. Because melanin derived from DHICA is able to better quench radical species, this melanin selection may be an important mechanism to protect human melanocytes from the toxic effects of DHI and other oxidative stresses.

The association of dysfunctional Q cycling in the pathogenesis of these two autoimmune diseases

a) Hydroquinone derivatives have long been topically used for treatment of pigmentation disorders in dermatology clinics. However, the effectiveness of hydroquinone was sometimes contraindicated and/or uncertain since topical creams are usually mixed with metal chelators that inhibit tyrosinase [19]. The pigmented eruptions from inflammatory skin conditions or wound repair are often decolored at first, but quickly regain color deposition with continued hydroquinone application. This observation at least suggests the possibility of using quinone products to rebuild pigmentation in the skin of VL-affected patients.
b) Occupational leukoderma has been reported in factory workers exposed to monobenzone [20] or other phenolic and catecholic compounds found in hair dyes, resins, adhesives, and leather manufacturing [21,22]. Vitiligo development was shown to occur in one group of workers working in food storage (specifically garlic

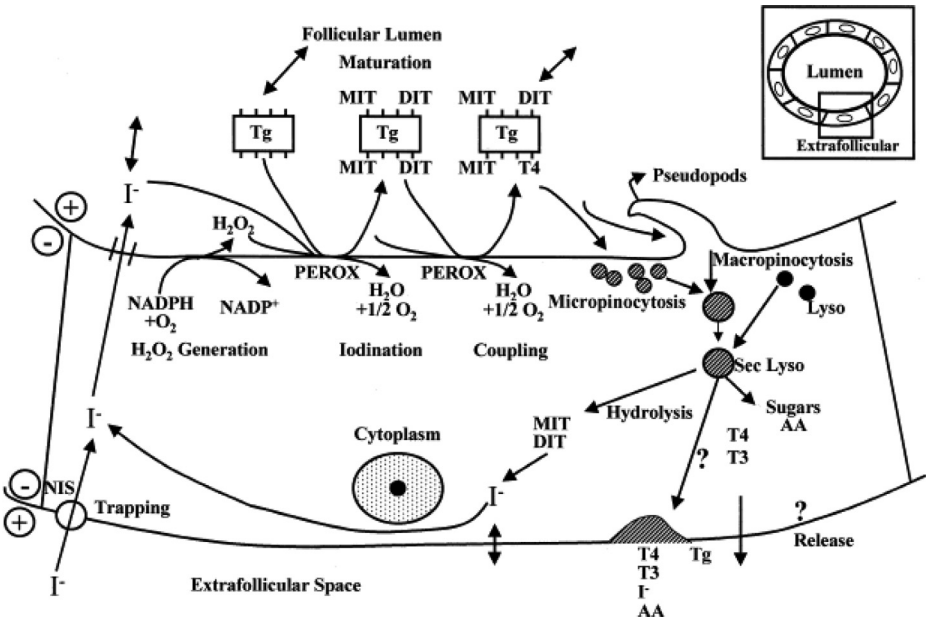

Fig. 4. Redox reactions involved in the synthesis of thyroid hormones, illustrating the role of H_2O_2 in these reactions.

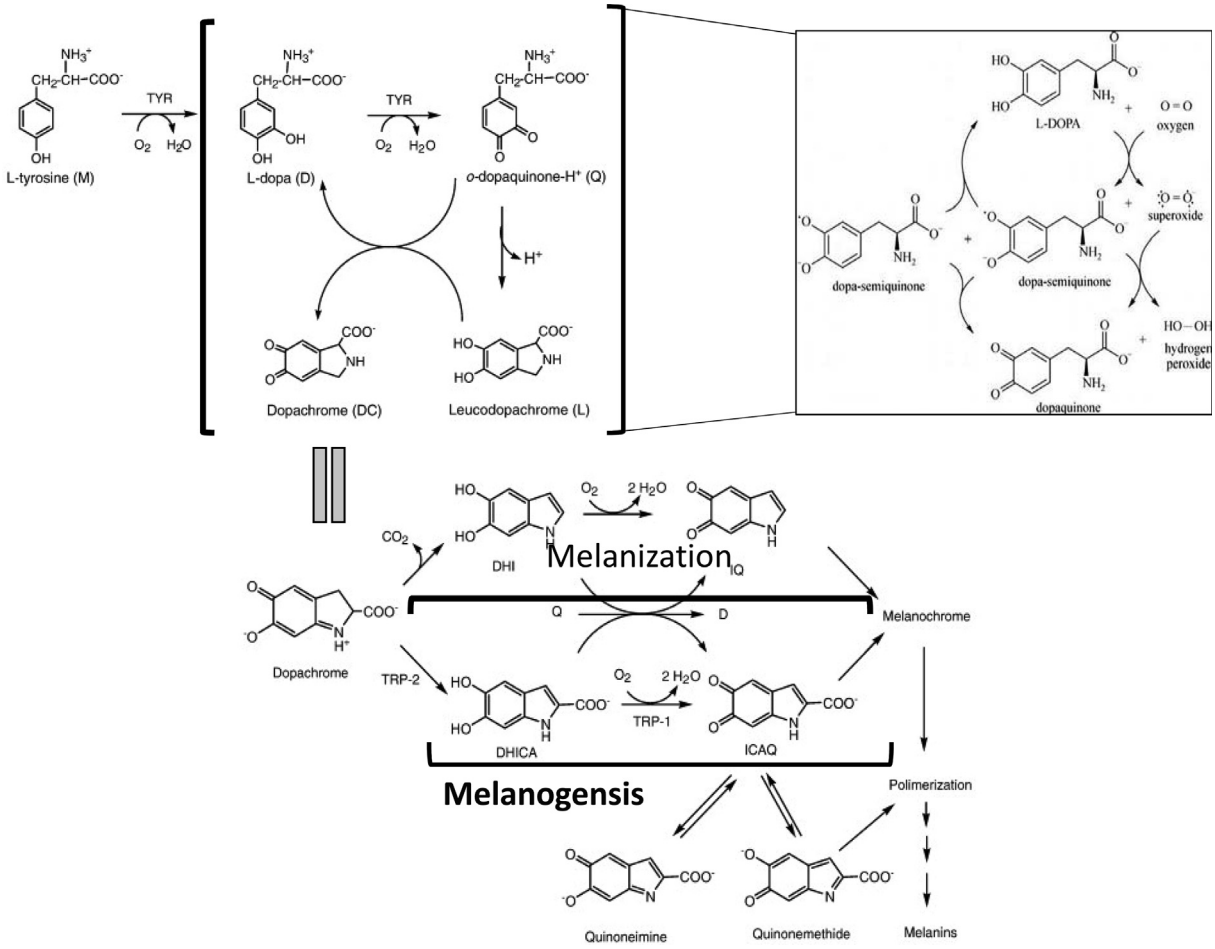

Fig. 5. Schematic representation of the enzymatic formation and conversion of diphenols (L-dopa, DHICA) to dopachrome (DC) and ICAQ, respectively, (two square brackets) are coupled to Q cycling and H_2O_2 formation, as shown in the inset diagram for L-dopa to dopachrome (modified from Ref. [18]). The melanogenesis branch from dopachrome is the dominant path for eumelanin synthesis.

storage) where ammonia gas was employed. This type of occupational vitiligo can be explained by the fact that amine radicals generated by the ammonia treatment are very active in the presence of phenolic compounds. If DHICA or even L-dopa is consumed by these amine-containing compounds, pigmentation polymerization is then inhibited due to a lack of substrate, which will lead to more serious sequelae for those vitiligo-susceptible individuals who are incapable of efficiently cycling Q or SQ^- back to QH_2 as described previously. This then would result in elevated concentrations of superoxide in melanocytes leading to their death. These aberrations have resulted in much higher frequencies of acquired vitiligo cases in post-industrial societies in general.

c) Mitochondrial-Q cycling may yet provide further support for the concurrent development of VL in a rare form of mitochondrial disorder. In a study by Karvonen et al. [23], an increased prevalence of vitiligo was found in patients with the bp 3243 mutation of mitochondrial DNA in the mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes syndrome (MELAS). As shown in Fig. 3, the perturbation of mitochondrial CIII in this disorder would lessen the likelihood of semiquinone cycling back to quinone or hydroquinone and therefore provide the molecular lesion proposed in the hypothesis.

d) A depletion of reduced form of $CoQ_{10}H_2$, but not the oxidized form CoQ_{10}, was observed in epidermal lesions of patients with active vitiligo together with a reduction of catalase [24]. According to the authors, an over-generation of pro-oxidant species accounts for the depletion of $CoQ_{10}H_2$. The normal level of CoQ_{10} suggests that the derangement is taking place between SQ^- and QH_2. The blockage of SQ^- transforming to QH_2 will accumulate partially reduced SQ^-, leading to increased oxidative stress and the reduction of $CoQ_{10}H_2$.

e) Amiodarone-induced thyroid disorder is one of side reactions of this highly effective antiarrhythmic agent due to its similarity in chemical structure with thyroxine [25]. One could posit that the hypothyroid conditions in these patients are caused by competition for iodine. However, plasma coenzyme Q10 concentrations are significantly lower than those in normal subjects [26], which suggests that the metabolism of amiodarone competes with thyroxine for the CoQ_{10} redox pool.

Evaluation of the hypothesis/idea

Since the proposed hypothesis was developed in light of known and published information, it makes predictions amenable to later investigation and confirmation. In this section, we describe how the hypothesis might be tested by clinical investigation using a proposed therapeutic regimen. As antioxidant enzymes such as catalase, superoxide dismutase and glutathione peroxides have been widely investigated in pathogenesis of ROS-induced apoptotic mechanisms in both diseases, we have focused on the effects of the low molecular weight antioxidants ubiquinol $CoQ_{10}H_2$ and glutathione (GSH). The latter is involved in the removal of quinones and in the induction of quinone reductase.

Experimental studies and clinical data

In order to test our hypothesis we propose an *in vitro* investigation of quinone metabolism in melanocytes and thyrocytes in cell lines derived from both normal and affected patients, as well as an *in vivo* treatment regimen in an animal model system. The testing platform consists of 1) normal and pathologic behaviors of two types of cellular responses (i.e., morphologic, pathologic); 2) qualitative determination of different quinone species (HPLC); 3) quantitative measurement of the levels of biosynthetic products in two types of cells; and 4) mitochondrial enzymatic assays [27]. The monolayer and floating culture systems are developed and are in wide current use for investigation of these two types of cells [28,29]. The following testing parameters are proposed: 1) the cells or animals treated with reduced quinone such as $CoQ_{10}H_2$, n2-hydroxybenzyl alcohol (2HBA), 3-hydroxybenzyl alcohol (3HBA) 4-hydroxybenzyl alcohol (4HBA), other hydroquinone (HQ) and GSH; 2) the cells or animals treated with oxidative stress inducers such as menadione and 2,3-dimethoxyl-1,4-naphthoquinone (DMNQ); 3) the cells or animals treated with mitochondrial CIII inhibitor (antimycin); and 4) cells or animals treated with NAD(P)H quinone oxidoreductase NQO1 inhibitor (dicumarol).

The study of clinical biopsy samples is also suggested for direct measurement of the different quinone species in patients suffering both separately and concurrently from these diseases. Gene sequencing is proposed with emphasis on studies of cytochrome proteins in cells obtained from peripheral blood sampling.

Therapeutic use of quinone derivatives to combat ROS induced autoimmunity mechanism

CoQ10 deficiencies have been reported in patients with thyroid disorders [30,31]. As described previously, Q cycling links the classical pathways of bioenergetics in mitochondria with its antioxidant role in the body. Any condition that would increase oxidative stress – such as excessive UV radiation or chemical exposure – in patients with vitiligo and HT who already have compromised low antioxidant CoQ10 activity would be subjected to further damage and irreversible oxidative damage. The restoration of CoQ redox should therefore be therapeutically beneficial and should help restore normal anti-oxidative capacity and mitochondrial function as well.

The redox behavior of the quinone-hydroquinone system ($Q\text{-}QH_2$) has been the mechanistic basis for development of several pharmaceutical agents for the treatment of bacterial, parasitic and fungal infections as well as for malignancy. For example, anthraquinones (organic compounds found in some plants) remain a promising scaffold for the development of new drug candidates for the treatment of acute leukemia, malignant lymphomas and breast cancer [32]. Paradoxically, the one-electron reduction of anthraquinone that provides its therapeutic effectiveness, also leads to cardiotoxicity and chromosomal damage within normal cells due to the interruption of the mitochondrial respiratory chain by superoxide and other free radicals [33]. However, these effects not only require constant vigilance when interrupting Q cycling, but also provide important biomarkers of disorders of Q cycling in ROS genesis and mitochondrial function.

What is the advantage of the proposed therapeutic regimens directed at preserving quinone over current therapeutic schedules?

Current treatment for both vitiligo and autoimmune thyroid disease simply provide therapies with limited anti-inflammatory regimen or the replacement of deficient products, (e.g., topical corticosteroids or phototherapy or thyroxine replacement, respectively). They do very little or nothing to directly address ongoing autoimmune damage mediated by the oxidative stress-mediated toxicity. The proposed therapy, which is directed to the root causes of these diseases, therefore, offers several advantages. Caution should be exercised particularly with the use of immunomodulators as suggested by Rashighi et al. [34], since their immune compromising effects may lead to the development of melanoma. The optimal treatment strategy according to these authors should include the following: 1) normalizing the stress in affected cells, thereby directly minimizing or eliminating the direct sequelae of oxidative stress-mediated toxicity, 2) inhibiting autoimmunity and 3) promoting regeneration of melanocytes. While some progress has been achieved with strategies 2 and 3, the proposed use of antioxidants to block the onset and continued ongoing damage of disease as described under strategy 1 has only been poorly and inconsistently addressed.

Consequences of the hypothesis and discussion

Potential therapeutic usefulness of Coenzyme Q10 and other supplements in treatment of vitiligo and HT

The most common CoQ_{10} in human mitochondria is CoQ_{10} (Fig. 5). The quinone head is shown on the left with the 10 isoprene repeats in the tail. The following three rationales exist for the study of the possible protective roles of $CoQ_{10}H_2$ in the onset of both vitiligo and HT, or in the improved prognosis of each disease include the following: first, CoQ_{10} and its reduced form ubiquinol ($CoQ_{10}H_2$) are hyper-lipophilic and should provide maximal protection of cell membrane and lipoproteins from lipid peroxidation associated with UPR apoptotic destruction in both diseases. Second, CoQ_{10} is a safe supplement that has been widely used in clinical practice for chronic heart failure, neurodegenerative disease and anti-aging processes with minimal side effects. Finally, CoQ levels in biological fluids can be accurately assayed by HPLC using methods and parameters described by Mancini et al. [35], which allow measurement of comparative concentrations of reduced and oxidized forms of CoQ_{10} in patients, cell lines or experimental animal models.

In addition to hormonal supplementation, i.e., thyroxine or anti-immune agents, for autoimmune thyroiditis and vitiligo, respectively, the therapeutic approach of CoQ_{10} may start from 30 mg daily as suggested by Mano et al. [31]. Glutathione supplementation may be another therapeutic choice because of its antioxidant properties particularly for oxidized quinones. Minerals and other water-soluble ROS scavengers such as ascorbic acid may provide some additional benefits through their quinone anabolic effects [36,37,38].

Summary

The unique biochemical and biologic commonalities between melanocytes and thyrocytes not only make them vulnerable to the cellular destructive effects of continual oxidative stress but also amenable to the proposed therapy described in this report. In patients with vitiligo and autoimmune thyroiditis, additional environmental insults, such as exposure to UV or certain chemicals, e.g. phenolic and catecholic moieties, or any measures that increase superoxide formation, can rapidly deplete cellular redox resources and activities, which are already overwhelmingly pre-exhausted with the destructive effects of semiquinone and ROS molecules. In addition, the intrinsic genetic defects that reduce the body's capacity to defend against oxidant stress or restore normal redox function can further accelerate the death of melanocytes and thyrocytes in VL and HT patients by the activation of unfolded protein response (UPR) and innate inflammation [39,40,41].

Declaration of Competing Interest

None.

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