Biochimie 95 (2013) 436–444

Contents lists available at SciVerse ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Hypothesis

Is carotenoid ornamentation linked to the inner mitochondria membrane potential? A hypothesis for the maintenance of signal honesty

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ARTICLE INFO

Article history:
Received 29 June 2012
Accepted 26 October 2012
Available online 3 November 2012

Keywords:
Carotenoid oxidation
Ketolation
Coq biosynthesis
Mitochondria
Cotingins
Animal coloration

ABSTRACT

Several mechanistic hypotheses have been proposed for how carotenoid pigmentation of integumentary structures can serve as an honest signal of individual quality. These hypotheses are founded on proposed links between carotenoids, immuno responsiveness, and oxidative stress, but an absence of biochemical information on the oxidative pathways of carotenoids has limited the sophistication of such hypotheses. Based on published evidence, we propose that the oxidation of carotenoids for the purpose of ornamentation in birds and reptiles is coupled to the inner mitochondria membrane. We predict that several carotenoid oxidation reactions yielding ornamental pigments occur on the inner mitochondrial membrane. Three of these reactions are proposed to occur within the ubiquinone biosynthesis cluster known as the *Coq* cluster consisting of approximately a dozen *Coq* members, tightly integrated and intimately associated with Complex I and III of the electron transport system. Ubiquinone and highly oxidized ornamental carotenoids share a stereochemically-conserved binding region suggesting that these two molecules may have shared similar pathways in the past. Carotenoids and ubiquinones may cooperate as redox participants in anti-radical reactions or independently in helping to maintain membrane or supra-complex stabilization during times of high-energy demand. Under this hypothesis, oxidation of carotenoids is coupled to the inner mitochondria membrane potential such that ornamental coloration reflects the efficiency of cellular respiration.

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1. Introduction

Among the best-studied ornamental traits in animals are bright yellow, orange, and red color displays produced by deposition of carotenoid pigments in integumentary structures such as eyes, bills, skin, or feathers [1,2]. Current theory proposes that bright carotenoid displays are honest signals of individual quality [3,4] and abundant empirical evidence in many bird species supports an association between the showiness of carotenoid coloration and individual performance [5]. The mechanisms that link carotenoid ornamentation to performance, however, remain poorly understood [6].

Carotenoids cannot be synthesized by vertebrates *de novo*, so they must be sequestered in the diet [7]. In many birds, carotenoids are metabolized before they are deposited [2]. The majority of these reactions are oxidations (carotenoids lose electrons) while some may involve reductive hydride ($H:^-$) transfers (gains electrons). In this paper we will consider only oxidation reactions. Because carotenoids readily receive and transfer electrons, carotenoids are believed to serve as antioxidants within animal systems [8,9], and empirical studies consistently find links between oxidative stress, immunocompetence, and carotenoid intake [10,11]. These observations have led to the development of the Resource Tradeoff Hypothesis for the maintenance of honest signaling via carotenoid pigmentation [12–14]. By this hypothesis, carotenoids are essential and limiting resources serving as immuno-stimulants, antioxidants, and integumentary colorants, and only individuals with large pools of carotenoid resources are able to both maintain oxidative homeostasis and produce brightly colored integuments [15]. Alternatively, the Shared Pathway Hypothesis proposes that production of ornamental traits is fundamentally linked to vital cellular processes needed for general organism functionality [16]. By this latter hypothesis, carotenoid ornamentation is a direct indicator of the physiological state of the individual and is not simply a function of resource availability [17–19].

A shortcoming of both the Resource Tradeoff Hypothesis and the Shared Pathway Hypothesis is lack of specific cellular mechanisms. The locations and circumstances under which carotenoids might serve as critical antioxidants remain to be resolved even for model

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http://dx.doi.org/10.1016/j.biochi.2012.10.021

species like the laboratory mouse (*Mus musculus*) and are completely unexplored in vertebrates with integumentary ornamentation. Such vagueness has made the Resource Tradeoff Hypothesis difficult to critically assess but easy to support with statistical associations. Similarly, the specific pathways that are shared between vital cellular processes and mechanisms of ornament production have not been proposed for any color display.

In this paper we propose a biochemical model for the pathways that are shared in the production of cellular energy and the production of oxidized carotenoid pigments used in ornamentation. We propose that the oxidation of carotenoids occurs within the inner mitochondria membrane (IMM). We first highlight the similarities between carotenoids and ubiquinones in both structure and function. We next show that the pathways leading to UQ biosynthesis involve the same stereo-specific biochemical modifications required for carotenoid metabolism. We then explore the various core reactions of which ubiquinones are the principal redox participants. Finally, we introduce the IMM carotenoid oxidation hypothesis in detail providing supporting evidence from the literature. We conclude by considering the implications of linking ornamental coloration to cellular respiration for understanding both color signals and basic mitochondrial processes.

2. Structural and functional links between carotenoids and ubiquinone

Ubiquinone (UQ), also referred to as Coenzyme Q (CoQ_n), is best known for its role in aerobic respiration where it carries electrons and protons from the matrix side of the IMM to the inner mitochondria space (IMS). The movement of protons into the IMS provides the proton-motive force that drives ATP synthesis [20]. UQ has a multi-oxygenated aromatic planar ring and a ten-member (CoQ_{10}) isoprenoid or farnesyl tail (Fig. 1). The aromatic ring is redox active and the isoprenoid side chain is flexible enough to allow fluid movement within and across the bilayer leaflets and interaction with UQ binding sites. The redox-active aromatic end ring oscillates between the IMM surfaces accepting and transporting both protons and electrons [21,22]. Because UQ is especially lipophilic, it does not engage in radical transfer reactions with water-soluble anti-oxidants such as vitamin C and glutathione (GSH). If it is found outside the normal electron transfer pathways, however, it can interact with other lipophilic radical partners such as vitamin E (α-tocopherol) and carotenoids [23]. The aromatic ring of UQ derives from L-Tyrosine and L-Phenylalanine, and the isoprenoid tail is synthesized via condensation of isoprene monomers originating from acetyl Co-A via the mevalonate pathway [24]. In carotenogenic bacteria, plants, and fungi, carotenoids are also assembled via the mevalonate pathway and so share a part of their biosynthesis with prenylated quinones [24–26]. Unlike carotenoids, UQ is very difficult to assimilate in the diet due to its higher lipophilicity [27].

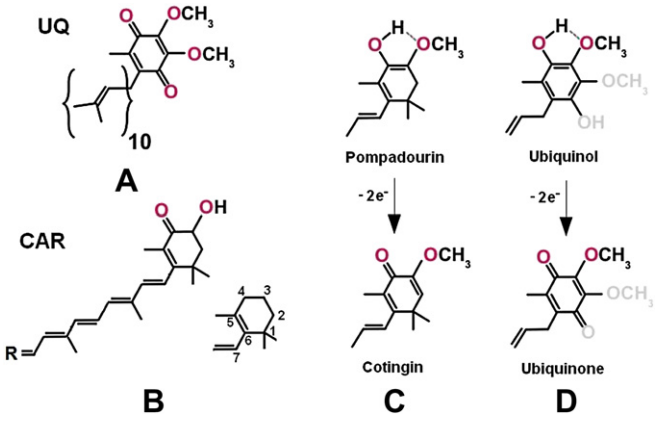

Fig. 1. Stereochemical representations of the end rings of ubiquinone (UQ), ubiquinol (UQH_2) and carotenoids (shown as one half a carotenoid in (B)). β-Ionone ring positions are numbered. UQ (A) has mirror symmetry across the end ring with the exception of the methyl group, which determines the binding configuration of this pigment with UQ redox complexes. The stereochemistry of the methyl group is maintained in carotenoids (B). Carotenoids with oxygenated functional groups (B) are considered xanthophylls; the removal of these hydroxyl groups convert them carotenes. Zeaxanthin can be converted to lutein (not shown) by relocation of the double bond within the β-ionone ring from position C5=C6 to C4=C5. Molecular mimicry can be seen in the oxidation of pompadourin to cotingin (C) when compared with the same oxidation of ubiquinol to ubiquinone (D).

Carotenoids are acquired by animals in their diets [1], and they fall into two major groups: xanthophylls and carotenes (Fig. 1). Two dietary carotenes (β,β-carotene, β,ε-carotene) as well as one dietary xanthophyll (β-cryptoxanthin) are pro-vitamin A carotenoids. Pro-vitamin A carotenoids are sequestered primarily for vitamin A homeostasis [28,29]. In all birds and some reptiles (turtles and most lizards), ingested carotenoids are subject to one or more rounds of oxidation leading to the production of some combination of canary xanthophylls, keto-carotenoids, and cotingins (involving the loss of 4, 8 or 12 electrons respectively across 2 end-rings) (Fig. 2). Several of these oxidation reactions of dietary carotenoids create the pigments that are used in oil droplets in the retina [30] and that are deposited to produce some of the most brilliant color displays in animals. Beyond precursor–product relationships, the biochemical natures of the oxidation reactions as well as the identities of the enzymes that catalyze these reactions remain completely unknown in animals. Like UQs, carotenoids actively interact with radicals undergoing both electron abstraction and electron transfer reactions, covering a wide range of anti- and pro-oxidant behavior [31].

2.1. Structural similarities of UQ and carotenoids

On first consideration, UQ and carotenoids appear to share few similarities in structure: UQ has an aromatic planar end-ring with a non-conjugated isoprenoid tail, and carotenoids have a weakly conjugated hexene end-ring with a conjugated isoprenoid backbone. UQ has an additional ketone at position C2 while carotenoids have a lipophilic dimethyl group in the same position. On closer inspection, however, the two ring systems share important similarities in molecular structure (Fig. 1). Using cotingin (a carotenoid pigment isolated from the feathers of the Pompadour cotinga, *Xipholena punicea* [32];) as a fully oxidized carotenoid to compare to UQ, we found that carbons C6–C5–C4–C3–C2 of the carotenoid ring system was stereochemically identical to the same sequence in UQ (Fig. 1). Astaxanthin (3,3′-dihydroxy-4,4′-diketo-β-carotene) mimics C6–C5–C4–C3 of UQ and retains the stereochemistry for binding (considering the four binding residues on UQ and electron transfer (ketone)). All three of these molecules are planar within the known binding sequence of UQ. This degree of similarity favors a potential for carotenoids and UQs to occupy similar binding sites. The single exception we found occurred at site Q_o in Complex III (ubiquinol-cytochrome c oxidoreductase, E.C. 1.10.2.2) (discussed below). In general we found that binding sites for the UQ ring and tail system within the various ETC complexes were accommodating (with sufficient volume) and appeared electrostatically compatible (with no apparent charge incompatibilities). Ohshima et al. [33] found the quinone reduction site at Complex I was spacious enough to accommodate bulky exogenous UQ analogs. This latter site was comparable in many ways to sites we inspected visually from available ETC 3D Protein Data Bank files revealing quinone binding (3H1J, 2WQY, 2H88 et al.).

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