Mitochondrial dysfunction: a neglected component of skin diseases

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Abstract: Aberrant mitochondrial structure and function influence tissue homeostasis and thereby contribute to multiple human disorders and ageing. Ten per cent of patients with primary mitochondrial disorders present skin manifestations that can be categorized into hair abnormalities, rashes, pigmentation abnormalities and acrocyanosis. Less attention has been paid to the fact that several disorders of the skin are linked to alterations of mitochondrial energy metabolism. This review article summarizes the contribution of mitochondrial pathology to both common and rare skin diseases. We explore the intriguing observation that a wide array of skin disorders presents with primary or secondary mitochondrial pathology and that a variety of molecular defects can cause dysfunctional mitochondria. Among them are mutations in mitochondrial- and nuclear DNA-encoded subunits and assembly factors of oxidative phosphorylation (OXPHOS) complexes; mutations in intermediate filament proteins involved in linking, moving and shaping of mitochondria; and disorders of mitochondrial DNA metabolism, fatty acid metabolism and heme synthesis. Thus, we assume that mitochondrial involvement is the rule rather than the exception in skin diseases. We conclude the article by discussing how improving mitochondrial function can be beneficial for aged skin and can be used as an adjunct therapy for certain skin disorders. Consideration of mitochondrial energy metabolism in the skin creates a new perspective for both dermatologists and experts in metabolic disease.

Key words: energy metabolism – mitochondria – OXPHOS – respiratory chain – skin

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Mitochondrial metabolism in the skin

The major function of mitochondria is to generate energy as ATP through oxidative phosphorylation (OXPHOS). In addition, mitochondria play important roles in heme synthesis, apoptosis and calcium homeostasis. In mitochondria, metabolites generated through breakdown of carbohydrates, proteins and fatty acids are fuelled into the citric acid cycle and OXPHOS to generate a proton gradient that is used to produce ATP via ATP synthase (complex V). Therefore, there are several levels at which defects can lead to diminished mitochondrial function and consequently to lower energy production.

The OXPHOS system is composed of multisubunit respiratory chain complexes I–IV, the F1F0 ATP synthase (complex V) and two electron carriers, coenzyme Q and cytochrome c. The subunits of the OXPHOS proteins are encoded by both mitochondrial and nuclear DNA. The mitochondrial DNA (mtDNA) contains genes for 13 OXPHOS polypeptides, 22 tRNAs and two ribosomal RNAs (1–3).

Emerging evidence suggests that mitochondria are vital regulators of skin physiology. Mitochondrial metabolism regulates keratinocyte differentiation by producing mitochondrial reactive oxygen species (ROS), which are necessary to propagate the Notch and β-catenin signals that promote epidermal differentiation and hair follicle development, respectively (4). Interestingly, a recent study proposed that epidermal progenitor/stem cells (EPSCs) are independent of the mitochondrial respiratory chain, but still require a functional dynamic mitochondrial compartment (5).

Mitochondria also play a role in melanocyte function and pigmentation. Prohibitin and complex V have been identified as modulators of pigmentation (6). Prohibitin has been functionally linked to many important cellular processes, including senescence and mitochondrial biogenesis.

However, mitochondria are also the major intracellular source of ROS, predominantly generated via complex I and III (7). ROS can inflict oxidative damage on biomolecules (e.g. proteins, lipids), resulting in loss of catalytic and/or structural integrity. With ageing, ROS-damaged proteins accumulate and OXPHOS activity declines.

Furthermore, ultraviolet (UV) radiation is known to induce oxidative stress in the skin (8,9), causing both nuclear and mtDNA damage, with the latter being a useful biomarker for both UV radiation exposure and extrinsic skin ageing (10–12). Indeed, Krutmann and Schroeder have proposed the ‘defective powerhouse’ model of premature skin ageing, where they adapted the free radical vicious cycle hypothesis for the skin, in which UV radiation-induced mtDNA deletions in dermal fibroblasts lead to inadequate energy supply, and retrograde mitochondrial signalling mechanisms give rise to functional and structural alterations in the skin (13,14). Thus, the mitochondria of skin cells can be damaged by both intrinsic and extrinsic assaults.

The purpose of this review is to provide the first comprehensive overview on mitochondrial function in skin diseases. In Table S1, we list the diseases and their associated mutations and clinical features as well as skin appearance. As the list of these diseases turned out to be astonishingly long and needing appropriate...
Classical mitochondrial diseases with skin involvement

Hair abnormalities and skin eruptions are part of the broad spectrum of presenting signs of mitochondrial diseases. Cultured human dermal fibroblasts can be used for diagnosing mitochondrial disorders in affected patients, thus indicating that dermal cells can express mitochondrial defects even these frequently do not cause obvious skin phenotypes. Skin alterations (scaly, pruritic, diffuse erythema with reticular pigmentation) have only been reported in some patients with Leigh syndrome, Pearson syndrome and mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome (15). A few case studies have demonstrated mtDNA mutations associated with a complex and severe skin phenotype (e.g. T3271C MELAS mutation and distal arthrogryposis; A3243G MELAS mutation in nail-patella syndrome) (16,17). Kearns Sayre syndrome is a mitochondrial multisystem disorder, usually associated with a single large deletion of mtDNA in muscle. Skin involvement (e.g. hypomelanosis) has also been shown in a few cases of Kearns Sayre syndrome (18–21).

Eight studies involving 101 subjects with Leigh syndrome caused by mutations in SURF1, an assembly factor of complex IV, revealed that 34% of the patients had hypertrichosis and 10% had hirsutism (22,23). An association of myoclonic epilepsy with ragged-red fibres (MERRF) syndrome and lipomas was reported (24–28).

Thus, there is no clear correlation between the OXPHOS complex that is affected and the clinical disease presentation, and no specific metabolic pattern has been detected among patients with primary mitochondrial diseases with skin manifestations versus those without.

Skin diseases associated with mitochondrial DNA alterations and variations

Non-epidermolytic palmoplantar keratoderma (NEPPK) is associated with mutations in different nuclear genes (Table S1), but interestingly also with the deafness-associated mtDNA mutation A7445G (29–32). A7445G simultaneously affects two mitochondrial genes, namely the precursor of mtDNA tRNA^ser(UCN) and complex IV subunit 1 (MT-COI) (Fig. 1) (30). Oxygen consumption in mutant cell lines is decreased, which could be explained by the fact that low levels of tRNA^ser(UCN) lead to lower levels of mtDNA-encoded OXPHOS subunits (33). The expression of MT-COI is not affected, as the mutation changes a stop codon (AGA) to an equivalent stop codon (AGG) (33).

Dupuytren’s disease is a familial fibroproliferative disorder affecting the hands. An autosomal recessive or maternal mode of inheritance was reported for only a very small number of patients. In patients with maternal inheritance, a 16S rRNA mutation in the mtDNA was detected (34–36). However, the functional relevance of the mutation has so far not been elucidated.

Somatic mtDNA mutations have been suggested to be associated with the development of melanoma and head and neck squamous cell carcinomas of the skin, as mutations have been found in almost every mitochondrial gene in those cancer types; details can be found in numerous reviews (37–43). However, the role of mtDNA mutations in cancer is contentious, because the majority of somatic mtDNA mutations in cancer tissues show low heteroplasmy, are functionally neutral or are of unclear functional relevance (44).

Common mitochondrial single nucleotide polymorphisms (mtSNPs) can be broadly categorized into mitochondrial haplogroup clades that reflect the ancestral matrilineal composition of populations. Common mitochondrial sequence variation and therefore mtDNA haplogroups may influence other common complex diseases. In melanoma patients, the frequencies of the major mitochondrial haplogroups did not differ significantly between patients and control subjects, whereas the frequencies of other SNPs located in the control region of the mtDNA were significantly higher in patients with melanoma compared to controls. Furthermore, mtSNPs were significantly associated with mean Bre-slow thickness and with metastasis. Therefore, mtDNA variations could be involved in melanoma aetiology and pathogenesis, although the relevance of control region polymorphisms in cancer remains to be elucidated (45).

Studies on a cohort of children with atopic dermatitis revealed an association between elevated IgE levels and mitochondrial European haplogroup U. Haplogroup U carriers showed trends of increased prick test reactivity and a higher frequency of atopic dermatitis (46).

Ras-mitogen-activated protein kinase (MAPK) pathway diseases

The Ras-MAPK signalling pathway is one of the most extensively studied signalling pathways and a large amount of data points to the involvement of this pathway in the regulation of mitochondrial physiology. Various syndromes of the MAPK pathway, including Noonan, cardio-facio-cutaneous, LEOPARD and Costello syndromes, are characterized by craniofacial dysmorphisms, heart defects, short stature and skin involvement (Table S1). In five unrelated children, who were initially diagnosed as having classical metabolic and clinical signs of an OXPHOS disorder, mutations in the Ras-MAPK pathway were identified, but the mutations could not explain the severity of the signs and symptoms. Further investigation showed the co-occurrence of mtDNA mutations in a subgroup of the patients, which could account for the differences in disease severity (47,48).
Approximately half of the patients with Noonan carry a gain-of-function mutation in the tyrosine phosphatase SHP2, a downstream regulator of ERK/MAPK. Recently, it was reported that SHP2 also localizes to the mitochondrial intercrystalline/intermembrane space, directly linking the MAPK pathway and OXPHOS (49). OXPHOS complexes might be targets of SHP2 as five tyrosine phosphorylation sites were identified in the cytochrome c oxidase, cytochrome c itself and the ATP synthase (50–55). In a SHP2 knock-down fibroblast cell line, a decreased protein expression of cytochrome c oxidase and cytochrome c was described. The cells exhibited a lower MMP and 30% lower ATP content, whereas ROS and catalase activity were significantly increased. Contradictory to the aforementioned data, the cytochrome c oxidase activity was increased (49).

**Skin diseases caused by mutation of nuclear genes encoding mitochondrial proteins**

The first disease in this section, anauetaxic dysplasia, is thematically linked to NEPPK in that it also results from a defect in mitochondrial RNA metabolism. Anauetaxic dysplasia, also known as cartilage hair hypoplasia (CHH), is caused by mutations in the RNA component of the mitochondrial RNA-processing ribonuclease (RMRP) (56). RMRP is an endonuclease that cleaves RNAs synthesized from the mtDNA origin of replication to produce RNA primers for leading strand DNA synthesis (57–59).

Two diseases can be regarded as OXPHOS complex assembly disorders (Fig. 2). The first, APLCC (aplasia cutis congenita, reticulolinial, with microcephaly, facial dysmorphism and other congenital anomalies), is caused by mutations in the nuclear COX7B gene, which encodes a structural subunit of complex IV (Table S1, Fig. 2). COX7B is indispensable for complex IV assembly and activity, and mitochondrial respiration (60). The second disease, Bjornstad syndrome, is caused by mutations in the BCS1L (BC1 ubiquinol–cytochrome c reductase) synthesis-like) protein, which facilitates the insertion of Rieske iron–sulphur protein into complex III during assembly (Fig. 2) (61). Defective BCS1L results in a catalytically inactive, structurally unstable complex III, subsequently leading to fragmentation of the mitochondrial network (62,63).

**Skin diseases associated with Fe-S cluster biogenesis and heme synthesis**

Heme synthesis (Fig. 3) and Fe-S cluster biogenesis are interconnected (64,65). Heme, which is needed as a prosthetic group in several important proteins such as cytochrome c, is partly synthesized in the mitochondrion (Fig. 3) (66–70). Mutations in the genes coding for enzymes in the heme synthesis pathway cause disorders characterized by photosensitivity and/or neurological symptoms, referred to as porphyrias. Photosensitivity of the skin seems to arise if the steps of heme b synthesis subsequent to generation of hydroxymethylbilane are affected (Fig. 3). The severity of photosensitivity appears to be lessened when the defects affect the mitochondrial reactions that follow the importation of coproporphyrinogen III (Fig. 3; Table S1). A light-sensitive dermatitis was reported for patients with ferrochelatase deficiency, the enzyme that catalyses the final step in heme synthesis (71).

Microphthalia syndromic 7 (MCOPPS7) is caused by mutations in the X-linked gene encoding mitochondrial holocytochrome c synthase (HCCS) that functions as a heme lyase (72). Loss of HCCS leads to lack of cytochrome c, which is an essential electron carrier in OXPHOS and apoptosis (Figs 2 and 3). It has been postulated that lack of cytochrome c disrupts the balance between apoptosis and necrosis and thereby damages affected tissues (73).

![Figure 2. OXPHOS system and complex assembly.](image-url)

![Figure 3. Importance of the heme biosynthetic pathway for skin diseases with mitochondrial involvement.](image-url)
Skin rashes and alopecia are signs of multiple carboxylase deficiency with juvenile onset caused by biotinidase mutations. Because one biotinidase isoform is localized inside mitochondria, mitochondrial biotin-dependent carboxylases (BDC), including pyruvate carboxylase, are affected by this disease (74). Thus, deficiency of biotinidase leads to severe ATP depletion (75). As BDCs also provide intermediates of the Krebs cycle for the synthesis of key metabolites such as heme or amino acids, biotin deficiency can cause heme deficiency (Fig. 3). Holocarboxylate synthetase deficiency, the neonatal or early-onset multiple carboxylase deficiency, is caused by mutations in the HLCS gene and characterized by skin rash and alopecia (76).

Menkes disease (MNK) is a fatal X-linked disorder characterized by a widespread defect in intracellular copper transport. The MNK gene (ATP7A) encodes a metal-transporting P-type adenosine triphosphatase. The MNK defect disturbs copper homeostasis and the functioning of copper-dependent enzymes such as superoxide dismutase and cytochrome c oxidase (Fig. 3) (77,78).

Disorders of fatty acid metabolism
Neutral lipid storage disease with ichthyosis (NLSDI) or Chanarin–Dorfman syndrome is caused by mutations in CGI-58 (comparative gene identification 58). Patients with mutations in the adipose triglyceride lipase (ATGL) gene also develop NLSD with myopathy but do not develop ichthyosis. Functional lipolysis depends on both ATGL and its cofactor CGI-58. Although mitochondrial morphology appeared normal in CGI-58 knockout mice, oxygen consumption and expression of master regulators of mitochondrial biogenesis were decreased in cardiac muscle (79,80). We propose that there is a similar mitochondrial phenotype in the skin of patients with NLSDI, but this remains to be demonstrated.

Congenital lipodystrophy is a rare cause of severe insulin resistance, in which mutations in proteins involved in adipocyte differentiation, fatty acid uptake, triglyceride synthesis and/or lipid droplet formation (Table S1) lead to a partial or generalized lack of adipose tissue and considerable accumulation of ectopic fat. Impairment of muscle OXPHOS was demonstrated by 31P-magnetic resonance spectroscopy measurements (81). Down-regulation of OXPHOS gene expression was observed in acquired partial lipodystrophy (Barraquer–Simons syndrome) in adipose tissue. It has been suggested that down-regulation of peroxisome proliferator-activated receptor γ (PPARγ), which serves as one of the master regulators of mitochondrial biogenesis, might be a general feature of lipodystrophies (82).

Disorders of intermediate filaments involved in mitochondrial tethering
Epidermolysis bullosa simplex (EBS) is characterized by recurrent blistering of the skin following minor physical trauma. Mutations of the plectin 1 (Plec1) gene cause EBS with muscular dystrophy (EBS-MD) (83). Plec1b, which localizes in the outer mitochondrial membrane, helps to maintain organelle shape and network formation by tethering mitochondria to intermediate filaments (84). In addition to disorganization of the intermediate filament network, severe mitochondrial dysfunction was reported in cells with Plec1 mutations; subsarcolemmal and intermyofibrillar proliferation of normal and abnormally shaped mitochondria were also observed. In patients with EBS-MD, complex IV and/or complex II negative fibres were identified, and decreased activity of complex I and complex IV was detected (85,86), thus contributing to the muscle phenotype. Interestingly, in keratinocytes of patients with EBS caused by mutation of keratin 5 or keratin 14, abnormal mitochondrial distribution was also reported (87).

Progeria syndromes
Hutchinson–Gilford progeria syndrome (HGPS) is caused by mutations in the lamin A gene, which is an intermediate filament protein comparable with plectin. Down-regulation of OXPHOS, especially the ATPase complex, accompanied by mitochondrial dysfunction was reported in HGPS fibroblasts, while glycolytic enzymes were up-regulated. Cytochrome c expression was diminished, and complex IV activity was significantly reduced, whereas mitochondrial biogenesis seemed unaffected in HGPS cells (88).

Autosomal recessive cutis laxa type IIB (ARCL2B) is caused by mutations in the pyrroline-5-carboxylate reductase 1 (PYCR1) gene. PYCR is a multimeric protein in mitochondria involved in de novo proline synthesis. PYCR1-deficient patient fibroblasts show altered mitochondrial membrane potential and increased fragmentation of the mitochondrial network (89–91).

A maternally transmitted lethal neonatal progeroid syndrome with low complex III and IV activity in muscle was reported. Three patients were noted to have several dysmorphic features, including hirsutism with a low anterior hair line extending to the forehead and cheeks (92).

Disorders of mtDNA repair
Many aspects of mtDNA repair remain enigmatic, although mitochondrial localization of nuclear repair enzymes has been demonstrated. Most of the proteins have pleiotropic functions, and interestingly, the nuclear and mitochondrial functions can be quite different.

Cockayne syndrome A (CSA) is caused by mutation of DNA excision repair protein 8 (ERCC8; CSA), and Cockayne syndrome B by mutation of ERCC6 (CSB) (93–95). Scheibye-Knudsen et al. (96) already summarized the striking clinical similarities between CSA and mitochondrial diseases in their article ‘Mitochondrial deficiency in Cockayne syndrome’. It was suggested that CSB is a disorder of DNA repair also affecting mtDNA, because mitochondrial base excision repair is reduced. Recently, evidence emerged that CSB might also be a disorder of mitochondrial transcription (96–100).

Rothmund–Thomson syndrome is caused by mutations in the helicase RECQL4 (RecQ protein-like 4), which can localize to mitochondria. Accumulation of mtDNA damage, decreased mtDNA integrity and increased mtDNA copy number have all been reported (101,102). The increase in mtDNA copy number might be a compensatory mechanism to counteract the mtDNA damage. Up-regulation of OXPHOS enzymes or mitochondrial biogenesis is frequently observed in patients with mitochondrial disorders. Thus, oncogenic tumors harbouring pathogenic complex I mutations show an immense compensatory increase in mitochondrial mass (103).

Werner syndrome is caused by mutation of RECQL2 (RecQ protein-like 2). The RecQ DNA ligase seems to be a repressor of hypoxia-inducible factor-1α (HIF-1α), a master regulator of energy metabolism that responds to hypoxia by inducing glycolysis. Loss of RECQL2 leads to HIF-1α stabilization and increased mitochondrial ROS production (104).

Ataxia telangiectasia (AT) is caused by mutations in the ataxia telangiectasia mutated (ATM) gene, a master mediator of the DNA damage response to double-strand breaks. ATM loss leads to...
defective mtDNA repair, reduced mtDNA integrity, reduction of DNA ligase III, altered mitochondrial morphology, deficiency in electron transport enzyme activity and increased mitochondrial mass caused by dysregulation of mitophagy (105–108).

Fanconi anaemia complementation group A is caused by mutation of FANCA. FANCA mutants show defective respiration through complex I, diminished ATP production and metabolic disturbance with an increased AMP/ATP ratio (109). However, a clear picture of the altered biochemical phenotype in Fanconi anaemia is still elusive, and the final biochemical defect(s) is still unknown (109–111).

Telomere shortening occurs during ageing, and recent evidence suggests that telomere metabolism and mitochondrial metabolism are interconnected (112–114). Thus, dyskeratosis congenita, which is caused by mutations in telomerase RNA component (TERC) and telomerase reverse transcriptase (TERT), is likely to exhibit mitochondrial alterations. Other syndromes caused by mutations in DNA repair components and presenting a skin phenotype might also be linked to mitochondrial dysfunction. For example, Bloom syndrome, trichothiodystrophy and xeroderma pigmentosum are candidates for mitochondrial alterations (115,116).

**Disorder of the deoxynucleoside triphosphates pool**

Aicardi–Goutiéres syndrome (AGS) type 5, also named chilblain lupus 2, shows overlap with systemic lupus erythematosus (SLE). The disease mimics a congenital infection (117) because it results from mutation of SAMHD1 (sterile alpha motif and HD-domain containing protein 1), which is part of the innate immune system. SAMHD1 is a triphosphohydrolase that converts deoxyribonucleoside triphosphates (dNTPs) to deoxynucleosides, and knockout of SAMHD1 leads to an increase in the cellular dGTP pool. Imbalanced dNTP pools decrease the fidelity of DNA polymerases and increase mutation rates. A balanced dNTP pool is also important for mitochondrial replication (118). Accordingly, multiple heterogeneous mtDNA deletions were found in liver and muscle of AGS type 5 patients (119,120). Complex I deficiency in muscle and an additional complex IV reduction in fibroblasts of a patient with AGS were reported (121).

**Autoimmune skin diseases**

Some autoimmune diseases of the skin are associated with increased levels of antimitochondrial antibodies (mtABs) such as pemphigus vulgaris and SLE. Alterations of mitochondrial energy metabolism in immune cells of SLE patients have been reported (122–126). T lymphocytes of patients with SLE exhibit mitochondrial hyperpolarization, increased ROS production and ATP depletion (125). MtABs against at least 25 mitochondrial proteins were found in patients with pemphigus vulgaris. Kalantari-Dehagi et al. proposed that mtABs are critical to pemphigus vulgaris pathology, rather than a bystander phenomenon (127–129). Normal keratinocytes cultured in sera from patients with pemphigus vulgaris displayed altered oxygen respiration, aberrant OXPHOS function and increased ROS production. The mitochondrion-protective drugs nicotinamide, minocycline and cycloporsine A were able to protect keratinocytes from the effects of pemphigus vulgaris-derived mtABs. Autoantibodies directed against mitochondrial proteins were also found in localized scleroderma (130). Most patients with mtABs exhibit generalized morphea with multiple plaque lesions but without linear lesions (131).

**Metabolic adaptation of cancer**

Aerobic glycolysis (Warburg effect) is a metabolic signature of many tumor types, including melanoma. Thus, serum lactate dehydrogenase (LDH) is a prognostic factor for patients with stage IV melanoma. However, the results of several studies indicate that melanoma may be unique in terms of energy metabolism among solid tumors, as OXPHOS seems to be preserved in melanoma (132), whereas it is reduced in a wide range of other solid tumors (133–135). Recently, it was demonstrated that the V600E BRAF oncogene (commonly found in melanomas) induces glycolysis and dysfunctional OXPHOS via an uncoupling mechanism (136). As most studies have used melanoma cell lines, further functional analysis of primary tumor tissue is required to elucidate mitochondrial function in melanoma in vivo. The main function of glycolysis in melanomas may not be to provide energy, but to generate molecules for biosynthetic pathways (137,138).

Basal cell carcinoma (BCC) is the most common cutaneous malignancy, and like other tumors, it possesses a heterogeneous genetic composition. Analysis of BCC microarray expression data revealed that several genes which are consistently down-regulated in tumor samples are involved in mitochondrial function, including OXPHOS. One of these genes encodes an accessory component of OXPHOS complex I that is essential for respiratory activity (139).

Birt-Hogg-Dubé (BHD) is characterized by skin fibrofolliculomas, lung cysts, spontaneous pneumothorax and renal cancer. The association of benign cutaneous lesions and increased cancer risk is also a feature of Cowden syndrome, an autosomal dominant disease caused by PTEN mutations. Patients with BHD and Cowden syndrome may develop oncocytomas, rare neoplasias that are phenotypically characterized by prominent mitochondrial hyperplasia. Oncocytomas frequently exhibit pathogenic mtDNA mutations in complex I genes (130,140–142).

**Therapeutic targeting of mitochondria**

Efforts aimed at rescuing mitochondrial function or inducing mitochondrial biogenesis should be considered in the treatment of a wide range of skin diseases. Accordingly, pharmacological agents that protect mitochondria (e.g. minocycline, nicotinamide and cycloporsine A) have been shown to have a beneficial effect on pemphigus vulgaris progression (129). Dithranol, a mitochondrial uncoupler that damages mitochondria, has a positive effect in psoriasis (143). It is interesting to note that in pemphigus vulgaris, an increase in mitochondrial fitness has a beneficial effect, whereas in psoriasis, damaging of mitochondria leads to improvement of skin physiology.

Oligomycin and aurovertin B were shown to correct albinism through binding to complex V. The mechanism involved inhibition of H+ transport by complex V, resulting in alkalization of the cytoplasm, a trigger for melanogenesis (6). Therefore, inhibition of OXPHOS might be used for the correction of hypopigmentation.

Glucocorticoids that are used to treat pemphigus vulgaris, SLE and psoriasis, and retinoids that are used to treat psoriasis all have dose-dependent effects on mitochondrial function. Long-term administration of low-dose corticosterone enhances mitochondrial oxidation and increases mitochondrial membrane potential, whereas high doses attenuate mitochondrial function and reduce the levels of mitochondrial anti-apoptotic proteins (144). Upon glucocorticoid treatment, glucocorticoid receptors translocate to...
mitochondria where they either induce mitochondrial gene expression or trigger apoptotic signalling (145–147).

Retinoids are also able to induce mitochondrial gene expression. In addition to nuclear genes, mitochondrial encoded genes have been reported to be regulated by retinoic acid (148). In cells deprived of retinol, respiration and ATP synthesis default to basal levels. Mitochondrial biogenesis and function can also be regulated via endogenous substances such as hormones and peptides. Some of most potent compounds involved in the control of energy metabolism are hormones of the thyroid axis such as thyroid-releasing hormone (TRH), thyroid-stimulating hormone (TSH), thyroxine T₃ and triiodothyronine T₄ (149–154). Both TSH and TRH are expressed in human skin and are potent regulators of mitochondrial biogenesis and consequently show activity in organ-cultured normal human epidermis (152). Mitochondrial biology, energy metabolism and redox state of human hair follicles are subject to profound (neuro-)endocrine regulation by hypothalamic–pituitary–thyroid axis hormones T₃ and T₄ (154). The neuroendocrine control of mitochondrial biology needs to be further explored for therapeutic applications in diseases with mitochondrial OXPHOS dysfunction.

Inclusion of bioactive molecules into skin care products able to trigger mitochondrial biogenesis to enhance overall aerobic energy metabolism in dermal cells would seem an appealing idea especially in aged skin, which shows as any other organ an age-dependent decline of mitochondrial function due to accumulating damage to mtDNA. However, the proportion of dysfunctional mitochondria might also be increased by this approach. As (defective) mitochondria are a rich source of ROS, higher mitochondrial mass might also promote oxidative stress, counteracting any beneficial effect of the treatment.

Nevertheless, some compounds used in personal care such as coenzyme Q10 (CoQ10) and nicotinamide have indeed demonstrated beneficial effects on mitochondria. Nicotinamide has the ability to lower ROS production in fibroblasts. CoQ10 has been reported to have beneficial effects on both clinical outcome and biochemical measures in mitochondrial disorders (155). CoQ10 treatment prevents mitophagy and improves mitochondrial function in human skin in vivo (156). Most strikingly, CoQ10 also prevents disruption of mitochondrial function following UV irradiation.

Exposure of normal human skin to UV light leads to an increase of a specific deletion of the mtDNA followed by reductions in oxygen consumption, mitochondrial membrane potential and ATP content. Interestingly, supplementation with the energy precursor creatine protects against age-related mutations of mtDNA in human skin cells (157). Creatine is frequently used for therapy of muscle diseases.

Conclusion
Skin involvement can be expected in primary mitochondrial diseases as a consequence of the numerous ATP-dependent processes occurring in the skin. Nevertheless, mitochondrialopathies that include major dermatological involvement are rare or not recognized as the severity of symptoms in other organs discrafts from less severe clinical features of the skin. Currently, it is unclear why only in rare cases of patients with primary mitochondrial disease, severe skin manifestations occur. On the other hand, observation of skin involvement could lead the clinician to suspect mitochondrial disease in currently undiagnosed patients. In contrast, a wide range of common skin diseases is associated with alterations in mitochondria-related metabolic pathways at different levels, and we expect that there are many more to be discovered.

Currently, for most diseases, we cannot discriminate which mitochondrial alterations are secondary to a primary dysfunction and where the mitochondrial dysfunction contributes substantially to the pathophysiology. Further research will be necessary to elucidate the exact alterations of the mitochondrial energy metabolism in some of the diseases as well as the contribution of the mitochondrial dysfunction to the onset and progression of skin diseases.

Mitochondrial pathologies might be targets of novel therapeutic interventions, as stabilization and stimulation of mitochondrial ATP production have potential as prophylactic and therapeutic measures in skin disorders. Furthermore, the knowledge of mitochondrial involvement now can explain the therapeutic efficacy of well-known drugs such as nicotinamide and minocycline in pemphigus. Influencing oxidative metabolism in the skin could also have implications for skin ageing and tumor development.

This review should sensitize the dermatologist to the importance of mitochondria, the ‘powerhouses of the cell’, for proper skin function.

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Author contribution
All authors designed and wrote the paper.

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Supporting Information

Additional supporting data may be found in the supplementary information of this article:

Table S1. Mitochondrial alterations in skin disorders and disorders associated with skin.