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## Oxidative phosphorylation inducers fight pathological angiogenesis

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**Pathological mutations in subunits of the oxidative phosphorylation (OXPHOS) system, or inhibitors of this biochemical pathway, increase the production of vascular endothelial growth factor (VEGF) and pathological angiogenesis. In many angiogenesis-related diseases, such as retinal, rheumatoid diseases, or cancer, OXPHOS dysfunction can be found. Thus, enhancing OXPHOS might be a promising therapeutic approach for pathologic angiogenesis.**

### Introduction

The neovascular form of age-related macular degeneration (nAMD) is a disorder that affects the macular region of the retina and causes progressive loss of central vision. Age is the main risk factor, with nearly all nAMD cases occurring in patients over 60 years old. The disease is characterized by choroidal neovascularization, and intravitreal therapy with ranibizumab, an inhibitor of all VEGFA isoforms, is highly effective [1]. However, a meta-analysis of 1-year results pointed out that a saturation effect of treatment occurred following an optimal number of 6.8–7.2 intravitreal ranibizumab injections per year [2]. If this is the case, the increased injection number might reflect refractory cases that respond poorly to ranibizumab. In patients with nAMD, the mitochondrial DNA (mtDNA) genetic background or haplogroup also modifies the response to intravitreal ranibizumab therapy [3]. At 4 months, in all haplogroups, best corrected visual acuity and central foveal thickness (CFT) values were higher and lower than basal values, respectively.

There were no differences among genetic backgrounds. However, at 12 months, CFT values of patients from the HV and U haplogroups remained lower than basal values, whereas individuals from the JT haplogroup showed similar CFT values to those before treatment. Moreover, individuals from the U haplogroup showed 12-month CFT values that were significantly lower than those of JT haplogroup. However, individuals from the JT haplogroup received a higher mean number of intravitreal injections (7.1) compared with the other haplogroups. Therefore, other approaches to treating nAMD should be looked for.

mtDNA haplogroups result in groups of phylogenetically related mtDNA genotypes. Particular combinations of mtDNA population polymorphisms define mtDNA haplogroups. mtDNA only encodes OXPHOS system subunits: seven from respiratory complex I (CI); one from CIII; three from CIV; and two from ATP synthase. It also encodes RNAs required for their expression. The 80 remaining OXPHOS subunits are encoded by nuclear DNA (nDNA). Thus, the

mtDNA haplogroup-defining genetic variants might affect OXPHOS function.

Therefore, evidence highlighting the association between mtDNA haplogroups and the clinical results of ranibizumab therapy in nAMD could be the result of a relationship between OXPHOS capacity and angiogenesis.

### **OXPHOS mutations and inhibitors increase VEGF production and pathological angiogenesis** *nDNA mutations*

Mutations in nDNA-encoded CII subunits result in decreased CII activity, increased VEGF mRNA expression, and stimulation of the angiogenic pathway in paraganglioma and pheochromocytoma tumors [4,5]. Similarly, mutations in the nDNA-encoded CIII subunit UQCRB also decreased OXPHOS function and increased VEGF mRNA and protein expression in UQCRB mutant transfected human embryonic kidney HEK293 cells [6].

Furthermore, vascular proliferation is a common feature of mitochondrial defects in

different tissues, notably in the central nervous system of patients with Leigh syndrome (LS) [7]. The genetic basis of LS is diverse and mutations causing this disease have been defined in many nDNA genes mainly associated with OXPHOS function, including CI (*NDUFV1*, 2; *NDUFS1*, 2, 3, 4, 7, 8; and *NDUFA1*, 2, 9, 10, 12), CIII (*UQCRCQ*), and CIV (*NDUFA4*) genes [8]. Nevertheless, LS also results from mtDNA mutations [8].

#### mtDNA mutations

Human SK-Hep1 hepatoma cells lacking mtDNA ( $\rho^0$  cells) express more VEGF mRNA and protein than parental cells with mtDNA,  $\rho^+$  cells. Moreover, conditioned medium from these  $\rho^0$  cells increased the formation of tube-like structures from human umbilical vein endothelial cells and new blood vessels in chorioallantoic membrane assays [9]. Mice expressing a mutant mtDNA polymerase showed mtDNA depletion, reduced OXPHOS enzyme activities, and increased expression of VEGF mRNA [10].

Transmitochondrial cell lines, cytoplasmic hybrids, or cybrids can be used to confidently link a phenotype to mtDNA mutations. These cells share nDNA and differ in their mtDNA. By using this model, it was shown that cybrids obtained from mouse Lewis lung carcinoma cells, harboring a CI mutation and having an OXPHOS defect, showed increased VEGF mRNA and protein levels and higher activity to induce neoangiogenesis than those with no mtDNA mutation [11,12].

In patients with mitochondrial myopathies attributable to heteroplasmic mtDNA mutations, in which mutated and wild-type mtDNA are present, muscle capillary density was twice that in sedentary healthy subjects and the capillary area was greatest in patients with the most severe muscle OXPHOS defects. It was also shown that, for each patient, capillary area around muscle fiber segments with defective OXPHOS function was more than twice that compared with muscle fiber segments with more preserved OXPHOS function. Lower and higher OXPHOS function likely mirror higher and lower percentage of mtDNA pathologic mutation, respectively [13].

In terms of visual disorders, an optic disc microangiopathy has been described as a typical ophthalmoscopic feature in patients who are asymptomatic for, or have, acute Leber hereditary optic neuropathy (LHON). LHON is an inherited form of vision loss that is caused by retinal ganglion cell dysfunction, mainly resulting from pathologic mutations in mtDNA genes. Interestingly, mtDNA J haplogroup increases the risk for LHON [14]. It was recently reported that,

when peripapillary capillary vessel density was normalized by retinal nerve fiber layer thickness, the vascular network in the temporal sectors was increased in unaffected patients with LHON mutation. This suggests that the metabolic consequences of retinal ganglion cell mitochondrial impairment result in a compensatory vascular response, primarily affecting the area of the papillomacular bundle [15].

#### OXPHOS inhibitors

Given these earlier observations, mitochondrial dysfunction because of OXPHOS inhibitors might elevate VEGF levels. Supporting this assertion, *in vitro* pretreatment of human adipose-derived stroma cells with CI or CIII inhibitors (rotenone or antimycin, respectively) increased VEGF secretion. Following their injection into mice, the angiographic score and capillary density also increased [16]. Another CI inhibitor (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), frequently used to model Parkinson disease, also increased the number of VEGF-expressing neurons and of blood vessels in the substantia nigra of parkinsonian-rendered monkeys [17]. Treatment of human brain microvascular pericytes with the CIV inhibitor sodium cyanide also resulted in increased expression of VEGF [18]. Hydrogen sulfide, another CIV inhibitor, also has proangiogenic effects [19]. The ATP synthase inhibitor oligomycin increased VEGF protein production in the human U-937 monocytic cell line [20]. Likewise, 4-hydroxy-2-nonenal increased mtDNA point mutations and reduced CIII and CIV activity and oxygen consumption in primary rheumatoid arthritis synovial fibroblasts (RASf). This compound also increased RASf VEGF immunofluorescence staining and VEGF secretion. The number of tube-like structures produced by human umbilical vein endothelial cells was also increased by 4-hydroxy-2-nonenal-treated RASf-conditioned medium [21].

#### Opposite observations

The earlier results suggest that OXPHOS deficiency promotes pathological angiogenesis. However, some results point in an opposite direction. For example, inhibition of the nDNA-encoded mitochondrial tryptophanyl-tRNA synthetase in endothelial cells reduced angiogenesis [22]; mutations in mtDNA-encoded tRNA genes decreased VEGF levels and angiogenesis [23,24]; inhibitors of mitochondrial translation (tigecycline and doxycycline) reduced neovascularization [25,26]; and rotenone and antimycin decreased VEGF production and angiogenesis in human ovarian cancer OVCAR-3, liver cancer HepG2 or mouse sarcoma-180 cells

[27,28]. Therefore, the relationship between pathological angiogenesis and OXPHOS function is complex and more studies are required for it to be fully understood.

#### Pathological angiogenesis is a feature of many OXPHOS disorders

Pathological angiogenesis can be observed in a range of disorders [29,30], such as ocular [31,32], rheumatic diseases [33,34], or cancer [35,36]. This might share a common early cause in these disorders. Thus, hypoxia appears to be the stimulus for retinal [37,38], synovial [39,40], or tumoral [41] angiogenesis. An essential adaptation to sustained hypoxia is the repression of mitochondrial respiration [42–44]. Angiogenesis frequently occurs in cancer, but nonangiogenic tumours can grow without triggering new vessel formation. Energy metabolism varies between angiogenic and nonangiogenic tumours. The latter show higher expression of proteins associated with OXPHOS and mitochondrial biogenesis [45,46]. It might be that OXPHOS dysfunction explains why pathological angiogenesis occurs in these diseases.

Primary OXPHOS disorders, such as those mentioned earlier, are not common [47]. However, many prevalent diseases are secondary OXPHOS disorders [48]. Mitochondrial alterations are often found in many of these angiogenesis-related disorders. Thus, retinal pigment epithelium from patients with AMD shows a decrease in the number and area of mitochondria compared with age-matched controls [49]. Mitochondrial oxygen consumption was significantly lower in retinal pigment epithelium from donors with AMD [50]. Mitochondrial number and COXIV protein levels were diminished in high glucose-cultured bovine retina endothelial cells. Moreover, in diabetic mouse retina or retina from patients with proliferative diabetic retinopathy, mtDNA was damaged and mtDNA copy number, mtDNA-encoded genes mRNA amount, nDNA-encoded COXIV protein levels, and citrate synthase activity were all decreased [51]. In rheumatoid arthritis (RA), synovial fibroblasts undergo a shift in ATP generation from OXPHOS to glycolysis, which could be an adaptation to the joint microenvironment, similar to that seen in tumor cells [40,52,53]. Regarding cancer, mtDNA mutations are common and tumor growth is promoted by mtDNA mutations affecting OXPHOS function [54–56].

If an important OXPHOS dysfunction can increase pathological angiogenesis, then mtDNA haplogroup-associated OXPHOS variation might be a susceptibility and/or resistance factor for

aspects of these angiogenesis-related diseases. For example, OXPHOS capability was lower in cybrids from the JT haplogroup [57] and OXPHOS electron transport rate was higher in cybrids from the U haplogroup [58]. Interestingly, the JT haplogroup appears to be a susceptibility factor for nAMD [59], and individuals from this haplogroup showed a worse response to nAMD intravitreal ranibizumab therapy [3]. By contrast, the U haplogroup appears to be a resistance factor for proliferative diabetic retinopathy [60,61], and individuals from this haplogroup showed a better response to nAMD intravitreal ranibizumab therapy [3]. In RA, radiographic erosions were significantly associated with the JT haplogroup [62] and, in early RA, an association was reported between erosions and increased intra-articular blood flow [63]. The mtDNA haplogroup has also been related to cancer risk [64–66].

Thus, these results suggest that OXPHOS function is impaired, and should be analyzed, in other angiogenesis-related disorders [29].

### Enhancing OXPHOS function would reduce pathological angiogenesis

If mechanisms underlying angiogenesis-dependent diseases are related, therapies for one disease might be helpful for others. OXPHOS dysfunction appears to contribute to these pathologies. Therefore, interventions to improve OXPHOS function would have widespread clinical applications. It was recently reported that the loss of  $\beta$ -adrenergic receptor signaling leads to inhibition of angiogenesis through enhancement of endothelial OXPHOS [67]. Also, the loss of the glycolytic isoenzyme pyruvate kinase M2 increased oxygen consumption rate and led to angiogenic sprouting defects [68]. Two main types of antiangiogenic drug have been developed: (i) monoclonal antibodies, or related molecules, targeting either VEGF or the extracellular domain of its receptor; and (ii) tyrosine-kinase inhibitors (TKI), targeting the intracellular kinase domains of VEGF, or other, tyrosine kinase receptors. It was recently shown that monoclonal antibody-related molecules increased the respiration rate in human adult retinal pigment epithelial-19 (ARPE-19) cells [69]. Moreover, it was also shown that tumor metabolism was reprogrammed in response to TKI, with increased mitochondrial metabolism. Thus, TKI-treated tumor tissue had intense CI staining and its respiratory capacity was higher than that of control-treated tumor tissue [70].

Several agents have already been proposed that, by acting on different cell targets, increase mitochondrial biogenesis [14]. Some of these compounds also appear to be beneficial for

angiogenesis-related diseases. For example, caffeine [71,72]; polyphenols, such as curcumin, epigallocatechin gallate, quercetin, and resveratrol [73–76]; thiazolidinediones, such as rosiglitazone [77,78]; valproic acid [79,80];  $\Delta^9$ -tetrahydrocannabinol [81,82]; and  $\omega$ 3-polyunsaturated fatty acids, such as docosahexaenoic or eicosapentaenoic acids [83]. These compounds could be used, along with other antiangiogenic drugs, as adjuvants for either all patients with angiogenesis-related diseases or those belonging to a particular mtDNA haplogroup with a high genetic risk.

### Concluding remarks

This retrospective analysis reveals a previously unrecognized pattern, that OXPHOS dysfunction might be an etiological factor for pathological angiogenesis. These observations lead to a new hypothesis whereby OXPHOS inducers would be interesting candidate drugs for the treatment of diseases involving pathological angiogenesis. Nevertheless, angiogenesis-related diseases also include those in which angiogenesis is hampered [29]. In such cases, OXPHOS inhibitors might act as proangiogenic drugs.

### Acknowledgments

This work was supported by grants from the Instituto de Salud Carlos III (ISCIII) (PI17/00021 and PI17/00166), Departamento de Ciencia, Tecnología y Universidad del Gobierno de Aragón (Grupos de Referencia B33\_17R), and the FEDER Funding Program from the European Union. CIBERER is an initiative of the ISCIII. Sponsors did not have any role in the study design; in the collection, analysis, and interpretation of data; in writing of the report; and in the decision to submit the paper for publication.

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