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Editorial

Metabolic Imaging and Flavoprotein Fluorescence in Optic Neuropathies

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The retina and optic nerve are among the most metabolically active tissues in the body, and their function depends on healthy mitochondrial activity. In many optic neuropathies (from glaucoma to hereditary optic atrophies), disrupted metabolism and oxidative stress precede the loss of retinal ganglion cells (RGCs). Metabolic imaging – techniques that visualize cellular energy states in vivo – thus holds great promise in ophthalmology. Unlike conventional imaging that reveals late-stage structural damage, metabolic contrast can flag dysfunction early. One approach gaining traction is flavoprotein fluorescence (FPF) imaging: under blue illumination, oxidized mitochondrial flavoproteins (mainly FAD) naturally emit green autofluorescence. Since the fraction of oxidized FAD rises when electron transport falters, FPF provides a real-time readout of mitochondrial oxidative stress.

Flavoprotein autofluorescence can be captured with specialized fundus cameras. Pioneering studies have shown that retinal FA increases with age and in diseases driven by oxidative stress. For example, older adults and patients with diabetes or macular degeneration exhibit elevated FA long before overt cell death. Importantly, FPF signals arise from living cells under stress (they cannot be elicited from already-dead cells), making this a sensitive early marker. Unlike lipofuscin-based autofluorescence, FPF is distinct and mitochondrial-specific. In fact, retinal layers with the highest mitochondrial density – the nerve fiber layer and ganglion cell layer – are bright in FPF, underscoring its relevance to optic nerve health. In sum, FPF imaging is a novel noninvasive metabolic biomarker: higher FPF intensity (and its spatial heterogeneity) correlates with RGC stress, potentially flagging optic neuropathy before vision loss.

Recent work has begun to validate FPF in patients. Using the latest generation retinal metabolic camera (OcuMet Beacon®), researchers have shown that FPF metrics robustly distinguish healthy eyes from those with retinal disease. Across cohorts of age-related macular degeneration, diabetic retinopathy, vein occlusion, and central serous retinopathy, elevated FPF intensity and heterogeneity were consistently seen in diseased eyes and tracked with visual acuity loss. In other words, a brighter and more nonuniform FPF signal corresponded to more severe pathology. These findings echo preliminary studies in glaucoma: for example, primary open-angle glaucoma eyes showed higher FPF at the optic nerve head, reflecting RGC mitochondrial dysfunction. As one recent review notes, "FPF can be utilized non-invasively as an indicator of mitochondrial oxidative stress in the retina" across conditions from glaucoma to macular disease. In practice, FPF can be quantified by average pixel intensity over the optic nerve or macula, and this number has diagnostic utility. Thus, metabolic imaging is moving rapidly from concept toward clinic.

Looking ahead, flavoprotein imaging offers exciting opportunities for early diagnosis and management. Because FPF abnormalities can emerge before any visible nerve thinning, this method could serve as an early warning system for optic neuropathies. Serial metabolic imaging may detect subclinical progression or responses to treatment in real time. Indeed, the ability to track mitochondrial health quantitatively opens the door to testing new therapies (antioxidants, gene therapies, etc.) and confirming their impact on retinal metabolism. As investigators conclude, FPF imaging may evolve into "a clinically useful means of assessing thera-

peutic impact of interventions aimed at reducing oxidative stress in the human retina". Likewise, larger longitudinal studies are already underway to establish FPF as a biomarker for disease monitoring and prognosis.

In conclusion, metabolic imaging by flavoprotein fluorescence is an emerging frontier in neuro-ophthalmology. By making mitochondria "visible", it adds a new dimension to eye diagnostics. This technique heralds the possibility that clinicians could detect and quantify optic nerve stress long before irreversible vision loss. As one recent perspective observes, innovations in retinal bioimaging "bring renewed hope that clinicians will soon be in a position to better monitor disease progression and improve the visual prognosis of patients with mitochondrial optic neuropathies". Ultimately, tracking flavoprotein signals may transform silent metabolic injury into actionable insight, offering patients and practitioners a brighter vision of the future.