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Editorial Open Access

Fumaric Acid Esters as Potential Therapies for Treating Degenerative Retinal Disease

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Editorial

Fumaric Acid Esters (FAE) are found naturally in some plants (*Fumaria officinalis*) and mushrooms. In Germany, a mixture of fumaric acid esters (Fumaderm®) is licensed for the treatment of psoriasis [1]. A clinical formulation of dimethyl fumarate (referred to as gastro-resistant Dimethyl Fumarate (DMF) or delayed-release DMF) is approved in the United States, New Zealand, Australia, European Union, Switzerland and Canada for the treatment of Multiple Sclerosis (MS) [2-5]. Immediately after oral intake, DMF is acted upon by intestinal esterases to form Monomethyl Fumarate (MMF); hence, MMF is the primary bioactive ingredient [6]. Following DMF ingestion, circulating MMF concentrations peak between 2-2.5 hrs and the half-life of the metabolite is around 12 hrs [7]. Recent studies have reported the use and potential efficacy of MMF in the treatment of various diseases other than those named above. Though quite heterogenous with respect to etiology, the common denominator amongst them all appears to be inflammation and oxidative stress. Inflammation and oxidative stress figure prominently in various degenerative diseases of the retina (i.e., diabetic retinopathy, sickle cell retinopathy, age-related macular degeneration and glaucoma). Given the impact of these factors on the development and progression of degenerative retinal diseases, others and we have evaluated the potential benefit of MMF in various *in vitro* and *in vivo* experimental conditions relevant to the pathogenesis of retinal disease.

In an early study, we showed MMF to be protective against reactive gliosis; folate uptake by Muller cells is considered a key event in this process [8]. MMF treatment significantly reduced folate uptake by Muller cells by decreasing the expression and activity of Proton-Coupled Folate Transporter (PCFT), a transporter integral to the uptake of folate. Based on these observations, it was proposed that MMF could be a potential candidate for the treatment of reactive gliosis, a characteristic response of Muller glial cells to an environment rich in pro-oxidant and inflammatory factors, in retinal disease. To determine whether in addition to down-regulating pro-inflammatory mechanisms, MMF affects counteractive or protective signalling, we evaluated the effect of MMF on the expression and activity of the cysteine/glutamate exchanger SLC7A11 (system x_c^-) [9]. Glutathione is the most abundant endogenous antioxidant in retina, and is therefore essential for protection of retinal cells against oxidative stress. System x_c^- is a transport system critical to the potentiation of antioxidant signalling in retina as it regulates the provision of cells with cysteine, an amino acid critical to glutathione production. Retinal pigment epithelial (RPE) cells are one of the major producers of glutathione therefore we exposed human retinal pigment epithelial (ARPE-19) cells to MMF in the presence or absence of pro-oxidant stimuli and evaluated the dose- and time-dependent effects on system x_c^- mRNA, protein, and activity levels. MMF treatment induced the up-regulation of each of these parameters. Additionally, MMF up-regulated hypoxia-inducible factor 1-alpha (Hif-1α) and nuclear factor erythroid 2-related factor 2 (Nrf2) expressions, and increased total glutathione (GSH) content. Collectively, our *in vitro* studies demonstrate that MMF affects multiple pathways in multiple retinal cell types in a manner that is overall protective against oxidative damage.

We next sought to evaluate the efficacy of MMF in a living animal model of retinal disease. Retinopathy is a major cause of vision loss in Sickle Cell Disease (SCD) and therapies to prevent and treat sickle retinopathy (SR) are very limited. Therapeutic induction of γ-globin expression and subsequent induction of fetal hemoglobin (HbF) production can alleviate some SCD-associated complications and Nrf2 inducers have been demonstrated to be effective γ-globin inducers [10]. The robust inductive properties of MMF on Nrf2 translocation and activity have been long recognized [11-13] and a prior study from our laboratory confirmed that, RPE cells, cells integral to retinal health and function, produce HbF [14], therefore it was logical to explore the effects of MMF in SCD. Indeed, MMF up-regulated the expression of γ-globin and associated HbF production both in RPE cell culture [14] and in a humanized mouse model of SCD [15]. Related *in vitro* studies toward elucidating the molecular mechanisms responsible for the MMF-induced improvements observed implicate Nrf2 and Bcl11A (B-cell lymphoma/leukemia 11A) as key players. Importantly, MMF treatment reduced the mRNA and protein expression of well-established markers of inflammation and oxidative stress (i.e., vascular endothelial growth factor, intercellular adhesion molecule-1, interleukin-1β, dihydroethidium labeling) and ameliorated retinopathy-like pathology in humanized SCD mice. Because high pressure liquid chromatography (HPLC) and hematological analyses of peripheral blood demonstrated reduced HbS content and white blood cell counts coupled with significant improvements in hematocrit, red blood cell number and hemoglobin concentrations in SCD mice that were treated with MMF, it is possible that fumaric acid ester therapy may be of benefit for non-retinal SCD-associated pathologies and/or SCD in general.

Recent work by Cho et al. [16] in a rodent model of retinal ischemia-reperfusion (I/R) injury are congruent with our findings and support a strong potential benefit for fumaric acid esters, specifically MMF, as therapeutic agents in retinal disease and, the relevance of Nrf2 activation in the process. MMF treatment was associated with significant increases in the expression of Nrf2-responsive antioxidant genes and a suppression of inflammatory responses as evidenced by increased expression of NAD(P)H quinone dehydrogenase 1, thioredoxin reductase 1 and hemeoxygenase-1 along with decrease in interlukin-1β, chemokine (C-C motif) ligand expressions [2,7,12]. Collectively, these molecular improvements interpreted to improve

retinal function as evidenced by electroretinogram recordings performed on live mice. In *Nrf2*$^{-/-}$ mice, MMF failed to elicit any antioxidant and/or anti-inflammatory response to protect mice against retinal I/R injury.

Like oxidative stress and inflammation, retinal ischemia induced neuronal degeneration is a major cause of visual impairment in various retinal diseases. Collectively, studies performed by others and ourselves strongly suggest that MMF could be a potential therapeutic agent under multiple conditions relevant to the development and progression of retinal disease. Importantly, the *in vivo* studies performed thus far involved the delivery of the drug through the gastrointestinal system (drinking water or intraperitoneal injection) and benefit was detected in retina. This is extremely significant and clinically important giving the known difficulties associated with drug delivery to the posterior segment of the eye (i.e., invasive delivery methods, poor sustainability in the absence of frequent administration, infection risk, etc.). Although much remains to be explored regarding the therapeutic role of MMF in treating various retinal diseases, preliminary results are encouraging. Additional detailed studies to evaluate the efficacy of fumaric acid esters in the treatment of specific retinal diseases are warranted. Since, DMF is currently approved for clinical use by the US-FDA, clinical studies exploring the potential of DMF in the prevention and treatment of retinal diseases holds high merits.

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