Proposed Mechanism of Long-Term Intraocular Pressure Lowering With the Bimatoprost Implant

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PURPOSE: The purpose of this study was to evaluate the effects of pharmacologically relevant bimatoprost and bimatoprost free acid (BFA) concentrations on matrix metalloproteinase (MMP) gene expression in cells from human aqueous outflow tissues.

METHODS: MMP gene expression by human trabecular meshwork (TM) , scleral fibroblast (SF) , and ciliary muscle (CM) cells exposed to 10 to 1000 µM bimatoprost or 0.1 to 10 µM BFA (intraocular concentrations after intracameral bimatoprost implant and topical bimatoprost dosing, respectively) was measured by polymerase chain reaction array.

RESULTS: Bimatoprost dose-dependently upregulated MMP1 and MMP14 mRNA in all cell types and MMP10 and MMP11 mRNA in TM and CM cells; in TM cells from normal eyes, mean MMP1 mRNA levels were 62.9-fold control levels at 1000 µM bimatoprost. BFA upregulated MMP1 mRNA only in TM and SF cells, to two- to three-fold control levels. The largest changes in extracellular matrix (ECM) -related gene expression by TM cells derived from normal (n = 6) or primary open-angle glaucoma (n = 3) eyes occurred with 1000 µM bimatoprost (statistically significant, ?50% change for 9-11 of 84 genes on the array, versus 1 gene wi

CONCLUSIONS: Bimatoprost and BFA had differential effects on MMP/ECM gene expression. Dramatic upregulation in MMP1 and downregulation of fibronectin, which occurred only with bimatoprost at high concentrations observed in bimatoprost implant-treated eyes, may promote sustained outflow tissue remodeling and long-term intraocular pressure reduction beyond the duration of intraocular drug bioavailability. Variability in bimatoprost-stimulated MMP upregulation among cell strains from different donors may help explain differential long-term responses of patients to bimatoprost implant.

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