PURPOSE: In early exudative age-related macular degeneration (AMD), segmental thinning of Bruch's membrane is associated with ingrowth of choroidal neovascularization into the subretinal space. To determine whether there is a link between oxidative stress and extracellular matrix (ECM) degradation by the retinal pigment epithelium, the present study focused on the effect of oxidative stress on MMP-1 and MMP-3 expression, two enzymes with substrate specificity for components of Bruch's membrane. METHODS: Cultured human RPE cells were exposed to oxidative stress. To investigate the role of signal transduction proteins, cells were pretreated with the specific inhibitors SB202190 or PD98059. Secreted MMP-1 and MMP-3 were detected by ELISA, MMP-2, and MMP-9 by zymography. Expression of mRNA was determined by quantitative real-time RT-PCR. ECM degradation by retinal pigment epithelium was assessed by immunofluorescence microscopy. RESULTS: Oxidative stress increased MMP-1 and MMP-3 protein release but reduced MMP-2 activity. Real-time RT-PCR disclosed increases of MMP-1 and MMP-3 mRNA after oxidative stress with no modulation of TIMP-1. MMP-2 and MMP-9 mRNA was slightly enhanced. PD98059, an inhibitor of ERK1/2, markedly reduced MMP-1 expression, whereas SB202190, an inhibitor of p38 MAPK, was less effective. MMP-3
expression was attenuated by both inhibitors. Oxidative stress-stimulated type I collagen degradation by RPE cells was reduced by simultaneous treatment with a synthetic MMP-inhibitor or a neutralizing antibody against MMP-1. CONCLUSIONS: MMP-1 and MMP-3 in the retinal pigment epithelium are inducible by oxidative stress. The directional shift in the MMP-1,-3/TIMP-1 ratio is associated with increased type I collagen degradation. This may be an important mechanism contributing to the pathogenesis of early exudative AMD.