The Proteasome Inhibitors Epoxomicin and MG262 Suppress Urokinase-Type Plasminogen Activator Expression by Human Oral Squamous Carcinoma Cells (HSC-3)

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We examined the effects of proteasome inhibitors, epoxomicin and MG262, on urokinase-type plasminogen activator (uPA) mRNA expression and uPA production in HSC-3 cells, a human oral squamous carcinoma cell line. Epoxomicin and MG262 suppressed uPA mRNA expression and uPA production in a dose-dependent manner. A time course study demonstrated a marked decrease in uPA mRNA expression from as early as 6 h after initiation of exposure to epoxomicin (50 nM) or MG262 (50 nM), and the suppressive effects were similar or a little stronger at 12 and 24 h. Epoxomicin and MG262 also decreased the transcriptional activity of nuclear factor (NF)-κB-dependent promoter. The inhibitory effect of MG262 on the constitutive NF-κB activity was stronger than that of epoxomicin. Because transcription of uPA gene is known to depend on NF-κB activity, the suppression of uPA gene expression by these proteasome inhibitors is conceivably mediated by inhibition of constitutive NF-κB activity. Furthermore, epoxomicin and MG262 reduced the invasive activity of HSC-3 cells. The suppressive effect of MG262 on the invasive activity was stronger than that of epoxomicin. The decrease in invasive activity by these proteasome inhibitors is at least partly mediated by the suppression of uPA production.

Key words : uPA, epoxomicin, MG262, NF-κB, oral squamous carcinoma cells

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