Lipopolysaccharide plus 12-o-tetradecanoylphorbol 13-acetate induction of migration and invasion of glioma cells in vitro and in vivo: Differential inhibitory effects of flavonoids.

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Abstract

Abstract—In an earlier study, we reported that nitric oxide is involved in lipopolysaccharide plus 12-o-tetradecanoylphorbol 13-acetate-induced malignant transformation via increases in metalloproteinase 9 enzyme activity and inducible nitric oxide synthase gene expression in rat glioma C6 cells,however the mechanism has remained undefined. Lipopolysaccharide plus 12-o-tetradecanoylphorbol 13-acetate, but not lipopolysaccharide or 12-o-tetradecanoylphorbol 13-acetate alone, induced transformation in glioma C6 cells (but not in human glioblastoma cells GBM-8401 cells) without affecting their viability. An increase in inducible nitric oxide synthase protein expression, nitric oxide production, and metalloproteinase 9 enzyme activity is identified lipopolysaccharide/12-o-tetradecanoylphorbol 13-acetate-treated C6 cells,however lipopolysaccharide/12-o-tetradecanoylphorbol 13-acetate and 12-o-tetradecanoylphorbol 13-acetate (but notlipopolysaccharide) addition shows the similar inductive pattern on metalloproteinase 9 enzyme activity without affecting inducible nitric oxide synthase protein expression and nitric oxide production in GBM-8401 cells. Treatment of C6 cells with lipopolysaccharide/12-o-tetradecanoylphorbol 13-acetate increases the expression of phosphorylated extracellular regulated protein kinases and Jun N-terminal kinases, but not p38, proteins, and an addition of the extracellular regulated protein kinases inhibitor PD98059 or Jun N-terminal kinases inhibitors SP600125, but not thep38 inhibitor SB203580, significantly blocked lipopolysaccharide/12-o-tetradecanoylphorbol 13-acetate-induced inducible nitric oxide synthase protein expression and metalloproteinase 9 enzyme activity accompanied by blocking morphological transformation in C6 cells. Among 19 structurally related flavonoids, kaempferol and wogonin exhibit significant inhibitory

effects on lipopolysaccharide/12-otetradecanoylphorbol 13-acetate-induced morphological transformation and colony formation, and attenuation of inducible nitric oxide synthase, phosphorylated extracellular regulated protein kinases protein expression, and metalloproteinase 9 enzyme activity was observed. 2=-OH flavone at a dose of 100M inhibition of lipopolysaccharide/12-o-tetradecanoylphorbol 13-acetate-induced events via apoptosis induction is identified. Furthermore, lipopolysaccharide/12-o-tetradecanoylphorbol 13-acetate, but not lipopolysaccharide or 12-o-tetradecanoylphorbol 13-acetate, induces tumoral invasion and migration in vitro and in vivo, and those are blocked by kaempferol and wogonin addition. These data suggest that combination of lipopolysaccharide and 12-o-tetradecanoylphorbol 13-acetate promotes tumoral progression via activating metalloproteinase 9 enzyme activity and inducible nitric oxide synthase gene expression, which is located downstream of mitogenactivated protein kinases activation, in rat glioma cells C6. Kaempferol and wogonin exhibit effective inhibitory effects on lipopolysaccharide/12-o-tetradecanoylphorbol 13-acetateinduced events, and thus possess the potential for further development.