LPS plus TPA induction of migration and invasion of glioma cells in vitro and in vivo: differential inhibitory effects of flavonoids.

陳彥州

SC Shen;CW Lin;HM Lee;LL Chien;YC Chen

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 not lipopolysaccharide) 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 the p38 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-o-tetradecanoylphorbol 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 100 microM 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 mitogen-activated protein kinases activation, in rat glioma

cells C6. Kaempferol and wogonin exhibit effective inhibitory effects on lipopolysaccharide/12-o-tetradecanoylphorbol 13-acetate-induced events, and thus possess the potential for further development.