Anti-angiogenesis mediated by angiostatin K1-3, K1-4 and K1-4.5. Involvement of p53, FasL, AKT and mRNA deregulation

吳銘斌

Chen YH;Wu HL;Li C;Huang YH;Chiang CW;Wu MP;Wu LW

摘要

Abstract

The molecular mechanism mediated by multiple forms of angiostatin via acting on proliferating vascular endothelium remains elusive. To address whether three forms of angiostatin, K1-3, K1-4 or K1-4.5, utilized similar or distinct pathways to mediate anti-angiogenesis, we adopted an adenoviral expression system to express secretable angiostatin molecules for CM collection. The anti-angiogenic activity of K1-3, K1-4 or K1-4.5 was confirmed by using proliferation, migration, tube formation and apoptotic assays of human endothelial cells. These angiostatin molecules at comparable expression level inhibited various in vitro angiogenesis assays with some variations. Furthermore, K1-3, K1-4 or K1-4.5 increased the expression of p53 protein and its downstream effectors, enhanced FasL-mediated signaling pathways, and decreased activation of AKT. At least three different receptors, Fas, integrin alpha(v)beta3 and ATP synthase, were involved in the anti-angiogenic action of angiostatin molecules. Besides, the expression of 189 genes at mRNA level was significantly altered by K1-3, K1-4 or K1-4.5. More than 70% of these genes participate in growth, inflammation, apoptosis, migration and extracellular matrix. Taken together, K1-3, K1-4 and K1-4.5, regardless of the number of kringles in the angiostatin molecules, mediated anti-angiogenesis via mostly similar pathways. We are the first to demonstrate the involvement of DAPK1 in the mediation of anti-angiogenesis by angiostatin.

.