論文審査の要旨

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Low grade inflammation inhibits VEGF induced HUVECs migration in p53 dependent manner

(小規模の炎症反応は、VEGF で誘導されるヒト血管内皮細胞の遊走能を p53 分子依存性に抑制する。)

Background: Endothelial cell migration is an important process for physiological angiogenesis which turns into pathological angiogenesis if not maintained properly. We intended to study the proteins involved in the process of crosstalk between inflammation and angiogenesis and their contribution in cell migration. We hypothesized that acute low grade inflammation must be involved in inhibiting angiogenesis in endothelial cells.

Method: We treated HUVECs with the proinflammatory factor TNFα and the angiogenic factor VEGF. We examined the impact of the treatment on cell migration, protein levels and subcellular localization of p53 and its regulating molecules.

Results: We have obtained following findings. (1) Acute low grade TNFα pretreatment inhibits VEGF-induced HUVEC migration. (2) Acute low grade TNFα pretreatment and VEGF co-incubation synergistically upregulated p53. (3) TNFα pretreatment also caused sustained nuclear localization of p53 even after VEGF co-incubation. (4) Silencing p53 caused increased cell migration compared to scramble. (5) p53 downregulated Id1 and inhibited its shuttling from the nucleus to the cytoplasm. (6) Downregulation of Id1 resulted in downregulation of β_3-integrin. (7) Similar results were seen in HCT116 cells which carry wild type p53 like HUVEC.

Discussion: Acute low grade inflammation has been used to treat bladder cancer in the past. We found a new insight on how acute low grade inflammation is capable of decreasing angiogenesis. Acute low grade inflammation upregulates p53 with VEGF synergistically. p53 inhibits Id1 which causes downregulation of β_3-integrin. Downregulation of β_3-integrin causes decrease in cell migration. However, cells must be carrying wild type p53 for the proposed signaling pathway.

以上のように、本研究は炎症と血管新生の関連を機能的・分子病態的側面から深く検証し考察したものである。特に小規模の炎症反応といった腫瘍進展時や慢性炎症下で想定される条件を、培養細胞において丁寧に再現・検証し、血管内皮細胞の遊走能を検討した。また、一般にがん抑制遺伝子として臨床・基礎で研究の盛んな p53 分子を基軸とした血管内皮細胞のシグナルを詳細に追跡し、一連の小規模炎症反応が遊走能を抑制するメカニズムの一端を見事に解明したことは、非常に学問的価値の大きいものである。よって本研究は学位論文として十分な価値を有するものと判定した。