MELANOMA AND MELANOCYTIC NAEVI

APIGENIN-INDUCED SUPPRESSION OF PD-L1 EXPRESSION EXERTS A DUAL EFFECT TO RESTRAIN MELANOMA GROWTH

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Background: The PD-L1/PD-1 pathway blockade-mediated immune therapy has shown promising efficacy in the treatment of multiple cancers including melanoma.

Objective: To reveal the growth-suppressive and pro-apoptotic functions of apigenin against melanoma cells, the present study examined the anti-tumor and immunomodulatory activities of apigenin towards melanoma using vitro and in vivo assays.

Methods: The influence of flavonoids on melanoma cell growth and apoptosis was investigated using cell proliferation and flow cytometric analyses. The differential IFN-γ-induced PD-L1 expression and STAT1 activation were examined in curcumin and apigenin-treated melanoma cells using immunoblotting or immunofluorescence assays. The effects of flavonoid treatment on melanoma sensitivity towards T cells were investigated using Jurkat cell killing, cytotoxicity, cell viability, and IL-2 secretion assays. Melanoma xenograft mouse model was used to assess the impact of flavonoids on tumorigenesis in vivo. Human peripheral blood mononuclear cells were used to examine the influence of flavonoids on PD-L1 expression in dendritic cells and cytotoxicity of cocultured cytokine-induced killer cells by cell killing assays.

Results: Curcumin and apigenin showed growth-suppressive and pro-apoptotic effects on melanoma cells. The IFN-γ-induced PD-L1 upregulation was significantly inhibited by flavonoids, especially apigenin, with correlated reductions in STAT1 phosphorylation. Apigenin-treated A375 cells exhibited increased sensitivity towards T cell-mediated killing. Apigenin also strongly inhibited A375 melanoma xenograft growth in vivo, with enhanced T cell infiltration into tumor tissues. PD-L1 expression in dendritic cells was reduced by apigenin, which potentiated the cytotoxicity of cocultured cytokine-induced killer cells against melanoma cells.

Conclusions: Apigenin restricted melanoma growth through multiple mechanisms, among which its suppression of PD-L1 expression exerted a dual effect via regulating both tumor and antigen presenting cells. Our findings provide novel insights into the anticancer effects

of apigenin and might have potential clinical implications.