Pharmacologically antagonizing the CXCR4-CXCL12 chemokine pathway with AMD3100 inhibits sunlight-induced skin cancer

Abstract

One way sunlight causes skin cancer is by suppressing anti-tumor immunity. A major mechanism involves altering mast cell migration via the C-X-C motif chemokine receptor 4–C-X-C motif chemokine ligand 12 (CXCR4-CXCL12) chemokine pathway. We have discovered that pharmacologically blocking this pathway with the CXCR4 antagonist AMD3100 prevents both UV radiation-induced immune suppression and skin cancer. The majority of control mice receiving UV-only developed histopathologically confirmed squamous cell carcinomas. In contrast, skin tumor incidence and burden was significantly lower in AMD3100-treated mice. Perhaps most striking was that AMD3100 completely prevented the outgrowth of latent tumors that occurred once UV irradiation ceased. AMD3100 protection from UV immunosuppression and skin cancer was associated with reduced mast cell infiltration into the skin, draining lymph nodes, and the tumor itself. Thus a major target of CXCR4 antagonism was the mast cell. Our results indicate that interfering with UV-induced CXCL12 by antagonizing CXCR4 significantly inhibits skin tumor development by blocking UV-induced effects on mast cells. Hence, the CXCR4-CXCL12 chemokine pathway is a novel therapeutic target in the prevention of UV-induced skin cancer.

Keyword: Sunlight; Skin cancer; Anti-tumor immunity; Sunlight-induced skin cancer