Keywords: chemokines, mast cells, skin cancer, immunosuppression, sunlight, ultraviolet radiation

Sunlight causes skin cancer by directly damaging DNA as well as by suppressing antitumor immune responses. A major mechanism whereby sunlight exerts immunosuppressive effects is by modulating the migration of chemokine (C-X-C motif) receptor 4 (CXCR4)-expressing dermal mast cells into and away from the skin. We have demonstrated the importance of this by showing that the systemic administration of the CXCR4 antagonist AMD3100 prevents sunlight-induced immunosuppression as well as the consequent carcinogenic response. Our results highlight the therapeutic potential of antagonizing CXCR4 signaling, especially in individuals who are at high risk of developing skin cancer.

Skin cancer is a growing clinical and economic problem that is primarily caused by the excessive exposure to the ultraviolet (UV) component of sunlight. In patients with severe sun damage as well as in solid organ transplant recipients (which are under immunosuppressive regimens), UV-induced squamous cell carcinoma (SCCs) is particularly aggressive and is associated with an extremely poor prognosis. Indeed, the SCCs that develop in these patients are not only more numerous than those arising in immunocompetent individuals, but also more likely to disseminate to distant organs. The successful prevention and treatment of these aggressive skin cancers require equally aggressive prevention strategies and therapeutic interventions. In turn, this requires a thorough understanding of the cellular and molecular mechanisms by which UV promotes the development of cutaneous malignancies. In addition to damaging the DNA of our skin, UV also suppresses antitumor immune responses. A critical player in this process is the dermal mast cell. While traditionally associated with atopic reactions, mast cells release anti-inflammatory cytokines that enable them to perform important immunoregulatory and anti-inflammatory functions. Indeed, the production of interleukin (IL)-10 by mast cells is required to prevent an excessive cutaneous inflammation in response to UV exposure. As a matter of fact, UV rays do not exert immunosuppressive effects in mast cell-deficient W/W^v or Kit^W^V^b mice, whereas the re-engraftment of mutant mice with wild-type bone marrow-derived mast cells restores the ability of UV to suppress adaptive immunity. We provided mechanistic insights into this process by demonstrating that dermal mast cells activated by UV rays migrate along a chemokine (C-X-C motif) ligand 12 (CXCL12) gradient that attracts them to nodal lymphocytes in a chemokine (C-X-C motif) receptor 4 (CXCR4)-dependent manner. This cellular rendezvous is a critical event because pharmacologically blocking the trafficking of mast cells to the lymph nodes by means of CXCR4 antagonist AMD3100 blocked the immunosuppressive effects of UV irradiation.

AMD3100 (Plerixafor, trade name Mozobil®) has recently been approved for mobilizing hematopoietic stem cells in hematological cancer patients prior to autologous transplantation. AMD3100 has also been shown to efficiently inhibit the growth of murine ovarian cancer as well as the metastatic dissemination of murine melanoma. The ability of AMD3100 to block the migration of mast cells has been linked to its capacity to suppress the growth of murine pancreatic ductal adenocarcinoma. Considering the central role that the migration of mast cells as induced by UV rays and the consequent immunosuppression play in skin carcinogenesis, we hypothesized that pharmacologically antagonizing CXCR4 with AMD3100 would also prevent UV-induced skin cancer. Indeed, we have recently demonstrated that this novel CXCR4 antagonist significantly protects mice from the development of sunlight-induced SCCs. The ability of AMD3100 to protect mice from chronic UV exposure-induced immunosuppression and carcinogenesis was associated with the inhibition of mast cell trafficking to the skin, the developing tumor and tumor-draining lymph nodes (Fig. 1). Orally supplied AMD3100 failed to affect peripheral
blood leukocytes, as well as any of the other CXCR4-expressing cells we investigated, including Ly6a<sup>+</sup> endothelial progenitor cells, FOXP3<sup>+</sup> regulatory T cells and myofibroblasts expressing α-smooth muscle actin.

Our findings have prominent clinical and societal implications. Indeed, although minimizing sun exposure is a useful strategy to reduce the incidence of skin cancer, this public health approach has failed to make a substantial dint in statistics. Perhaps, this is because we do not know the extent to which sun exposure would have to be decreased for the incidence of skin cancers to decrease. Genetic mutations and immunosuppression are both caused by less than half of the sunburning dose of sunlight, but the dose that promotes skin carcinogenesis in humans is unknown. The health-promoting effects of sunlight such as vitamin D production coupled to occupational and recreational activities might make it difficult to reduce cumulative sun exposure below a level that would substantially reduce the incidence of skin cancer, even with the use of sunscreens. Compelling evidence indicating that pharmacological strategies to prevent UV exposure-induced immunosuppression can protect humans from skin cancer has already been provided. Our data demonstrating that AMD3100 can prevent primary UV-induced skin cancers by selectively interfering with the ability of UV rays to modulate mast cell trafficking and consequent immunosuppression highlight the chemopreventive (and perhaps therapeutic) potential of antagonizing the CXCL12/CXCR4 signaling axis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Figure 1. Systemic treatment with the CXCR4-antagonist AMD3100 significantly protects from sunlight-induced skin cancer by modulating mast cell migration. The exposure of mice to 30 wk of sun-simulating UV (UVA + UVB) light resulted in the development of histopathologically confirmed squamous cell carcinomas (SCCs) associated with elevated levels of chemokine (C-X-C motif) receptor 4 (CXCR4). This was associated with a significant accumulation of mast cells not just into the irradiated dermis, but also into neoplastic lesions and tumor-draining lymph nodes. Such an alteration of the migratory pattern of mast cells did not occur in mice continually supplied with AMD3100 in the drinking water. Moreover, AMD3100-receiving mice were protected from the immunosuppressive effects of UV light and developed very few SCCs.
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