Reconstructive Surgery & Anaplastology

Short Communication

Modulation of aromatic hydrocarbon receptor (AhR) activity in the skin

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Abstract

Since 2016, the World Health Organisation has classified air environmental pollution as a major public health problem. The skin is the body's first line of defense against aggressions such as pathogens, toxins and harmful pollutants. The aryl hydrocarbon receptor (AhR) is a transcription factor playing a crucial role in skin defense. Indeed, AhR was initially described as a key chemo-sensor to environmental pollutants, as it regulates xenobiotic metabolism enzymes expression. It also plays an important role in the regulation of several genes involved in inflammation and immune response. However, prolonged activation of AhR by exogenous chemicals, such as Polycyclic Aromatic Hydrocarbons or dioxins, can lead to its deregulation and potentially to the development of skin diseases (atopic dermatitis, psoriasis and skin cancers). The aim of this project is to modulate AhR activity in the skin in order to develop innovative treatments using our non-competitive antagonist, MM107, synthesized by the PROTAC technique. In primary human keratinocytes, after AhR stimulation by an agonist, we observed by qRt-PCR that MM107 inhibited the induction of AhR target genes expression. These results were confirmed, at the protein level, for AhR itself and NF-κB. In addition, the catalytic activities of CYP1A1&1B1 and MMP1&13 were significantly decreased. MM107, in presence of an AhR agonist, also decreased the production of the pro-inflammatory cytokines TNF-α, IL-1β and IL-8; while increasing the anti-inflammatory cytokine TGF-β level. MM107, our proprietary molecule designed to specifically target AhR, could improve treatments of inflammatory skin diseases in which AhR has been involved.

Recently, the incident rate of skin cancer has been greatly increasing. The number of patients treated for skin cancers has increased by 44% during the past 5 years, and skin cancer has become the most common cancer type in Caucasians. Although both genetic and environmental factors contribute to the carcinogenesis of skin cancer, this rapid increase suggests the relative importance of environmental factors. The skin is the outermost interface between the body and the environment and is ineluctably exposed to environmental insults such as ultraviolet radiation (UVR) or air pollutants. As UVR and air pollutants can induce carcinogenesis in the skin , the skin contains a system that recognizes and detoxifies these carcinogenic insults, the dysregulation of which leads to the initiation of skin cancer. In addition to the increase in carcinogenesis of skin cancer, recent therapeutic aspects of skin cancer have greatly changed. In particular, the emergence of molecular targeted therapies including inhibitors for V600E mutated B-Raf proto-oncogene, serine/threonine kinase (BRAF) and checkpoint inhibitors, which attenuate suppression of the anti-tumor immune response, have drastically improved the outcome of advanced melanoma. These drugs retrogradely elucidated the critical contribution of specific proliferative signals and tumor immunity in the maintenance of melanoma. These recent changes in skin cancers imply the importance of identifying a key molecule that modulates carcinogenesis and maintains skin cancer to improve prevention of and therapy for skin cancers.

In addition to the carcinogenic role of AHR activation, AHR also greatly contributes to the maintenance of various skin cancers. In non-cutaneous tumors, AHR is an established factor that induces suppression of the anti-tumor immune response, resulting in the escape of tumor cells from immune-mediated cell death. Furthermore, AHR affects multiple aspects of cancer biology, including cell survival and proliferation. Recent findings show that AHR modulates anti-tumor immunity and proliferative signals in skin cancers. In the following sections, we introduce recent findings regarding how AHR contributes to the maintenance of skin cancers, mainly focusing on melanoma.

As summarized above, AHR was recently found to be a key modulator of UVR- and carcinogenic chemical-induced skin carcinogenesis. In addition, this molecule is associated with the efficacy of BRAF inhibitors and checkpoint inhibitors, which are core therapeutic drugs in melanoma. Taken together, these data underscore the importance of the AHR system in carcinogenesis and maintenance of skin cancers, especially SCC and melanoma. This means that the AHR system is a putative target, particularly for chemoprevention and cancer chemotherapy of skin cancer. The emergence of research investigating the effect of AHR antagonists for various skin cancers is promising and eagerly awaited.

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