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# Macrophage Migration Inhibitory Factor (MIF) Overexpression Accelerates Photocarcinogenesis in the Skin

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## 1. Introduction

The effects of sunlight have fascinated researchers for decades because nearly every living organism on earth is exposed to sunlight, including its ultraviolet (UV) fraction. UV radiation is divided into 3 subtypes, UVA (320–400nm), UVB (280–320nm) and UVC (200–280nm), each of which has distinct biological effects. Although UVC is blocked by stratospheric ozone, UVB (1–10%) and UVA (90–99%) reach the surface of the earth and cause skin damage (Matsumura and Ananthaswamy, 2002). An increased risk of skin damage from UV light has recently been linked to the decrease in stratospheric ozone (Ma et al., 2001). The health risks associated with ozone depletion are caused by enhanced UVA irradiation in the environment and increased penetration of the UVB light (Tenkate, 1999, Ma et al., 2001).

The skin is the body's main interface with the environment, and is frequently exposed to UV light. Exposure to UV radiation substantially increases the risk of actinic damage to the skin. UV irradiation leads to various acute deleterious cutaneous effects, including sunburn, as well as long-term consequences such as wrinkling, elastosis, irregular pigmentation, telangiectasia and the potential development of skin cancers (Young, 1990). In recent years, there has been increased interest in the contribution of UVA to skin carcinogenesis (Ridley et al., 2009). However, UVB has been demonstrated to be a causal factor for basal cell carcinoma, squamous cell carcinoma, and lentigo maligna in epidemiological and experimental studies, and UVB exposure has been shown to induce the superficial spread of melanoma in humans and other animals (Kraemer et al., 1997). Chronic UVB-induced inflammatory responses, immunosuppression, and direct DNA damage can be correlated with skin tumor formation (Fischer et al., 1999, Pentland et al., 1999). Furthermore, the inability to adequately repair DNA after UVB irradiation can result in the formation of skin cancers (Cleaver et al., 2002) (Figure 1).

## 2. Keratinocytes and UV-induced inflammatory cytokines

UV exposure can result in numerous changes in human skin, particularly on the face, neck, and arms. Keratinocytes, melanocytes, fibroblasts, and endothelial cells are all affected by

UV radiation. Epidermal cells are considered to be the major target of UVB radiation, as the vast majority of UVB is absorbed within the epidermis. There is emerging evidence that keratinocytes participate in cutaneous inflammatory reactions and immune responses by producing a variety of cytokines. UV irradiation may trigger cutaneous inflammatory responses by stimulating epidermal keratinocytes to produce biologically potent cytokines such as interleukin (IL)-1 (Ansel et al., 1988, Kupper et al., 1987), IL-6 (Kirnbauer et al., 1991), and tumor necrosis factor (TNF)- $\alpha$  (Köck et al., 1990). Once expressed, TNF- $\alpha$  affects a variety of cell types. It increases MHC class I expression on endothelial cells and dermal fibroblasts, induces the production of IL-1 $\alpha$  (Dinarello et al., 1986), increases the expression of adhesion molecules, including ICAM-1, VCAM-1 and E-selectin, and it promotes the formation of sunburn in cells (Schwarz et al., 1995). Furthermore, these cytokines are involved not only in the mediation of local inflammatory reactions but also play discrete roles in tumor promotion (Suganuma et al., 2002).

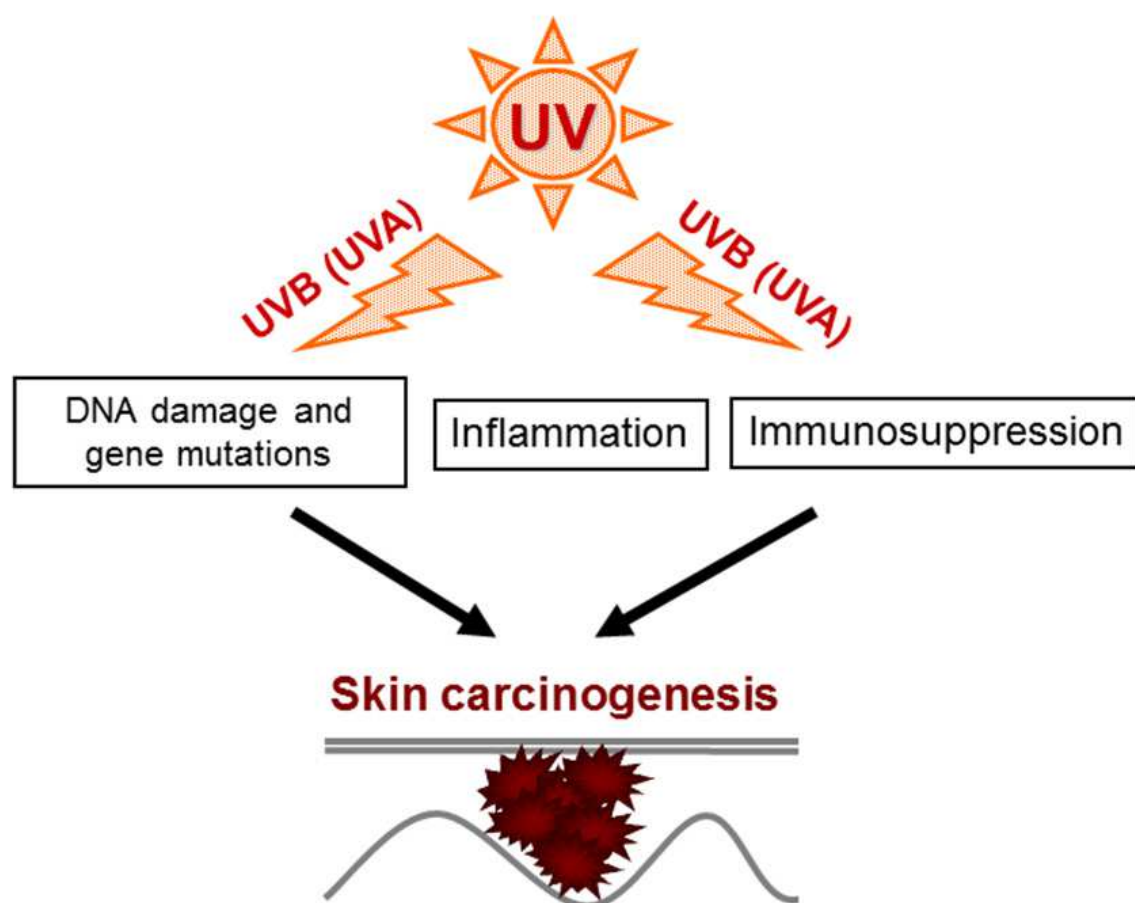


Fig. 1. UV-induced carcinogenesis in the skin.

UV radiation is carcinogenic because it induces DNA damage, gene mutation and chronic inflammation and has immunosuppressive effects on the skin.

UV radiation is also carcinogenic because of its immunosuppressive effect on the skin, and skin cancer patients have greater susceptibility to UV-induced immunosuppression (Streilein et al., 1994). The UV-induced keratinocyte-derived immunosuppressive mediators may enter the circulation and inhibit immune reactions in the skin-draining lymph nodes, or at skin areas

not directly exposed to UV radiation, thereby explaining the systemic immunosuppression often observed in skin cancer patients (de Gruijl, 2008). A major soluble factor involved in systemic UV-induced immunosuppression appears to be IL-10. UV-induced DNA damage can result in the release of IL-10, a potent immunosuppressive cytokine, from keratinocytes. It has been hypothesized that the production of IL-10 by keratinocytes or tumor-infiltrating cells may contribute to the immunosuppressive and anti-inflammatory effects, allowing them to escape the immune response (Salazar-Onfray et al., 1999, Weiss et al., 2004).

### 3. Macrophage Migration Inhibitory Factor (MIF) function in the skin

#### 3.1 Rediscovery of MIF

Macrophage Migration Inhibitory Factor (MIF) was originally identified as a lymphokine that concentrates macrophages at inflammatory loci. MIF is a potent activator of macrophages *in vivo* and is considered to play an important role in cell-mediated immunity (Bloom and Bennett, 1966, David, 1966). Since the molecular cloning of MIF cDNA, MIF has been reevaluated as a proinflammatory cytokine and pituitary-derived hormone that potentiates endotoxemia (Weiser et al., 1989). Subsequent work has shown that T cells and macrophages secrete MIF in response to glucocorticoids, as well as upon activation by various proinflammatory stimuli (Calandra et al., 1994). MIF has been reported to be primarily expressed in T cells and macrophages, however, recent studies have revealed this protein to be ubiquitously expressed by various other cell types, thus indicating that it has more far-reaching non-immunological role(s) in a variety of pathological states (Lanahan et al., 1992, Wistow et al., 1993, Bucala, 1996, Bacher et al., 1997, Nishihira, 2000).

MIF has broad activity on the induction of matrix metalloproteinases (Onodera et al., 2000), glucocorticoid-induced immunomodulation (Calandra et al., 1995), D-dopachrome tautomerase activity (Rosengren et al., 1996), innate immunity relevant to Toll-like receptor 4 (Roger et al., 2001) and is a crucial effector of hypoxia-inducible factor 1 $\alpha$  that delays senescence (Welford et al., 2006). It is known that MIF binds to the CD74 extracellular domain, a process that results in the initiation of a signaling pathway in a CD44-dependent manner (Shi et al., 2006, Leng et al., 2003). Recently, it was demonstrated that CD74 forms functional complexes with CXCR4 that mediate MIF-specific signaling (Schwartz et al., 2009). It has also been reported that a small-molecule MIF antagonist increased mesenchymal stem cell (MSC) migration (Barrilleaux et al., 2009). MIF may act on MSCs, at least in part, through CD74 (Barrilleaux et al., 2010). These recent findings suggest that MIF and its antagonists may have therapeutic applications in controlling MSC homing during repair of injury and in other clinically relevant situations.

#### 3.2 The role of MIF in the skin after UV radiation

In the skin, MIF is expressed in the epidermal keratinocytes and fibroblasts (Shimizu et al., 1996, Watanabe et al., 2004). MIF is known to play an important role in the skin with regard to inflammation, the immune response, cutaneous wound healing (Zhao et al., 2005, Dewor et al., 2007) and skin diseases, such as atopic dermatitis (Shimizu et al., 1999a, Hamasaka et al., 2009). In addition, skin melanoma cells express MIF mRNA and produce MIF protein (Shimizu et al., 1999b). The expression of MIF mRNA and the production of MIF protein have been shown to be substantially higher in human melanoma cells than in cultured normal melanocytes. Therefore, MIF functions as a novel growth factor that stimulates the uncontrolled growth and invasion of tumor cells (Shimizu et al., 1999b, Chesney et al., 1999, Shimizu, 2005) (Figure 2).

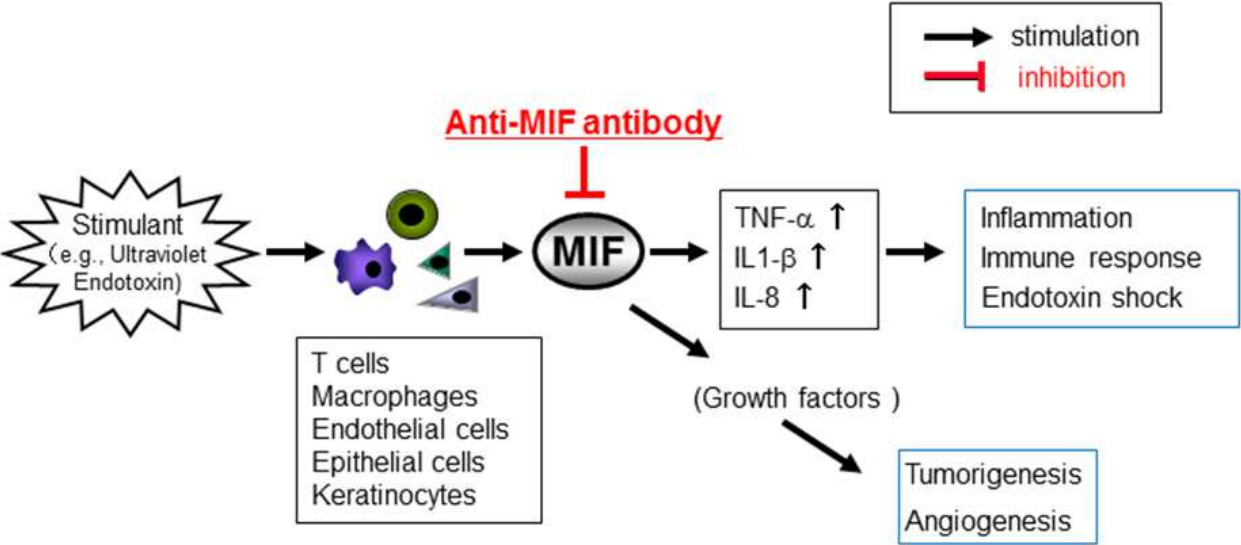


Fig. 2. Biological functions of MIF in the skin. MIF is readily released into the extracellular space and circulation in response to various stimuli, such as endotoxins and UV irradiation. MIF functions as a multifunctional cytokine, not only during inflammation and immune responses, but also during cell proliferation and angiogenesis. Anti-MIF antibodies effectively suppress these pathophysiological conditions.

Keratinocytes are capable of enhancing MIF production in the skin after UV radiation (Shimizu et al., 1999c). UV radiation indirectly regulates melanogenesis in melanocytes through a paracrine regulatory mechanism involving keratinocytes. Recently, it was demonstrated that the back skin of MIF transgenic (Tg) mice had a higher melanin content than that of wild-type (WT) mice after 12 weeks of UVB exposure. MIF mediated melanogenesis occurs mainly through the activation of protease-activated receptor-2 and stem cell factor expression in keratinocytes after exposure to UVB radiation (Enomoto et al., 2011). It has also been reported that MIF-deficient macrophages suppress the enhanced apoptosis and have restored proinflammatory function. MIF also inhibits p53 activity in macrophages via an autocrine regulatory pathway, thus resulting in a decrease in cellular p53 accumulation and subsequent function (Mitchell et al., 2002). Recent studies have therefore suggested a potentially broader role for MIF in growth regulation because of its ability to antagonize p53-mediated gene activation and apoptosis (Hudson et al., 1999, Nemajerova et al., 2007).

4. MIF and photocarcinogenesis

4.1 MIF and UV-induced gene mutations

Apoptosis and enhanced DNA repair are both mediated by the p53 tumor suppressor (Levine, 1997). The most commonly known UV-induced mutations occur in the p53 gene (TP53), and chronic UV exposure can increase the occurrence of TP53 mutations, leading to dysregulation of apoptosis, and the initiation of skin cancer (Stenback et al., 1998). UV-induced DNA lesions can lead to cell cycle arrest, DNA repair, and apoptosis if the DNA damage is beyond repair. In cells with wild type p53, UV radiation induces p53 expression, which in turn leads to increased p21 synthesis, which arrests the cell cycle in the S1 phase, enabling DNA repair to occur. However, p53 can also participate in the initiation and regulation of the DNA repair



process. In response to UV exposure, the protein bax is activated, which induces apoptosis and leads to the safe elimination of damaged cells. Therefore, it is important that apoptosis is induced immediately after UV irradiation. Any dysregulation in p53 signaling, especially with regard to its effects on the transcription of cell cycle regulatory and DNA damage response proteins, can result in cellular transformation.

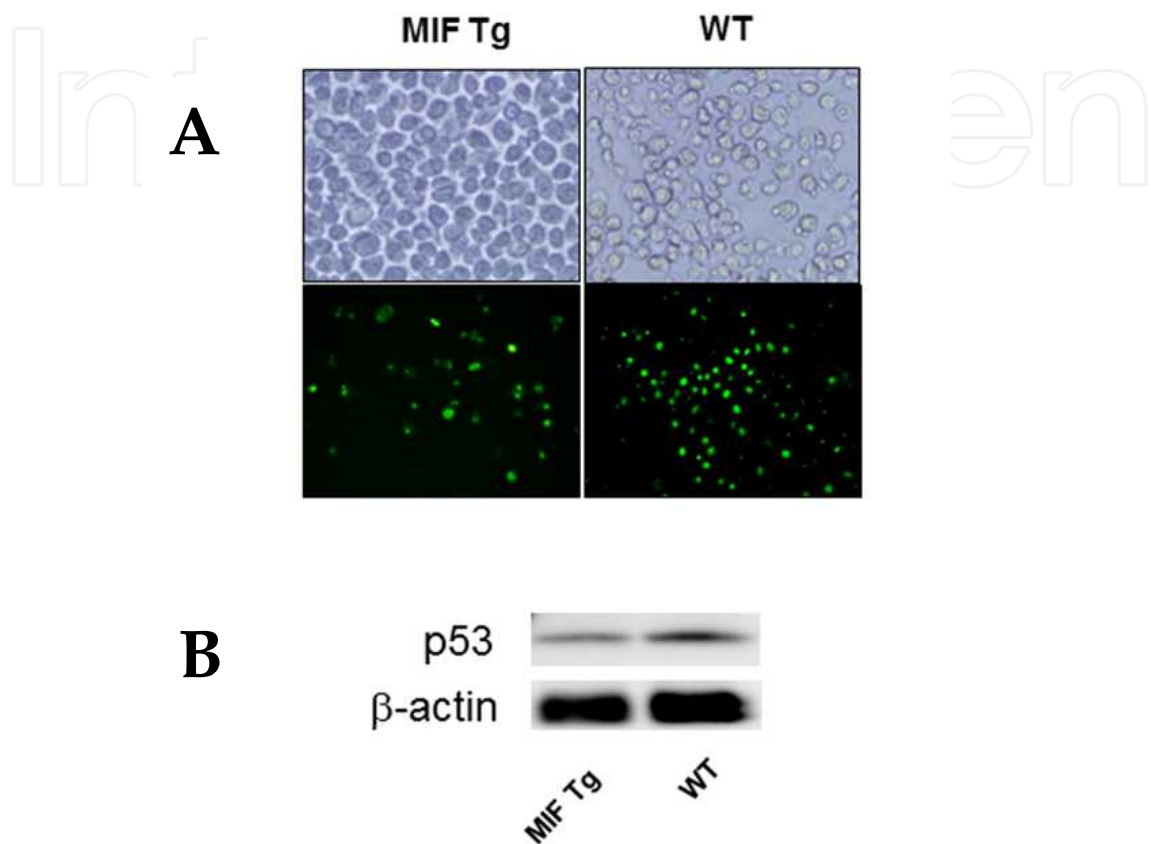


Fig. 3. UVB-induced apoptosis in cultured keratinocytes of MIF Tg and WT mice. (A) Cultured keratinocytes from the MIF Tg or WT mice were irradiated with UVB at 50 mJ/cm<sup>2</sup>, and the irradiated cells were analyzed by the TUNEL assay. The upper panels show morphological images. The lower panels show the results of the TUNEL assay. There were significantly fewer apoptotic keratinocytes (TUNEL positive) in MIF Tg mice than in WT mice ( $p < 0.005$ ). (B) The p53 protein expression of UVB irradiated keratinocytes was analyzed by a Western blot analysis. The p53 expression in the MIF Tg keratinocytes was lower than that of keratinocytes from WT mice.

MIF is a cytokine that not only plays a critical role in several inflammatory conditions but also inhibits the p53-dependent apoptotic processes (Fingerle-Rowson et al., 2003). Studies indicate that MIF treatment can overcome p53 activity and inhibit its transcriptional activity. Recently, it has been demonstrated that after chronic UVB irradiation, an early onset of carcinogenesis and a higher tumor incidence were observed in MIF Tg mice compared to WT mice (Honda et al., 2009). In addition, the UVB-induced apoptosis of epidermal keratinocytes was inhibited in the MIF Tg mice. Significantly fewer terminal deoxynucleotidyl transferase (TDT)-mediated dUTP-digoxigenin nick end labeling (TUNEL)-positive cells were detected in MIF Tg mice than in WT mice. There was also a decrease in the expression of apoptosis regulatory genes (i.e., p53 and bax), in the MIF Tg

mice after UVB irradiation (Figure 3). A previous study also demonstrated similar protective effects in the corneas of MIF Tg mice in response to acute UVB light (Kitaichi et al., 2008). MIF is upregulated by UVB irradiation in the mouse cornea, and MIF Tg mice showed fewer apoptotic corneal cells. Similarly, other studies have reported that MIF-deficient mice showed a significant increase in p53 activity and reduced tumor incidence compared to WT mice after acute and chronic exposure to UVB radiation, respectively (Martin et al., 2009). MIF has also been shown to have an inhibitory effect on UVB-induced photo-damage by blocking the expression of apoptosis-regulatory genes (Honda et al., 2009).

Recent evidence suggests that the pathways responsible for the removal of UV-mediated DNA damage can be modulated by several inflammatory cytokines. It has been observed that IL-12, which is an immunomodulatory cytokine, reduces UV-induced apoptosis *in vitro*. This was confirmed *in vivo*, because an injection of IL-12 into the skin of UV exposed mice significantly reduced the number of apoptotic keratinocytes (Schwarz et al., 2002). IL-18 seems to exert similar effects as IL-12. The injection of IL-18 into the UV exposed skin of mice reduced the amount of DNA damage (Schwarz et al., 2006).

#### 4.2 MIF overexpression accelerates photocarcinogenesis

In addition to decreasing protective DNA damage repair, MIF also exhibits direct pro-neoplastic activity. In many tumor cells and pre-tumor states, for example, in prostate (Meyer-Siegler et al., 1998), colon (Legendre et al., 2003), and hepatocellular cancers (Ren et al., 2003), adenocarcinomas of the lung (Kamimura et al., 2000), glioblastomas (Rogge, 2002), and melanomas (Shimizu, 1999b), increased MIF mRNA levels can be detected. The pro-neoplastic role of MIF has been studied by several groups. Fingerle *et al.* reported that embryonic fibroblasts from MIF-deficient mice exhibit p53-dependent growth alterations, increased p53 transcriptional activity, and resistance to ras-mediated transformation (Fingerle-Rowson et al., 2003). The concurrent deletion of the p53 gene *in vivo* reversed the observed phenotype of cells deficient in MIF. *In vivo* studies showed that fibrosarcomas are smaller in size and have a lower mitotic index in MIF-deficient mice relative to their WT counterparts. The authors concluded that there is direct evidence for a functional link between MIF and the p53 tumor suppressor (Fingerle-Rowson et al., 2003).

Using an anti-MIF antibody has also been reported to be effective for reducing tumor growth and neovascularization in lymphoma cells and vascular endothelial cells *in vivo* (Nishihira, 2000). Consistent with this finding, anti-MIF antibodies were found to be effective for reducing tumor angiogenesis in melanoma cells (Shimizu, 1999b). This was demonstrated *in vitro* by using recombinant MIF in fibroblasts, where growth-factor-induced stimulation of these cells resulted in increased MIF concentrations, activation of the extracellular regulated kinase/mitogen-activated protein (ERK-MAP) kinase pathway, and a subsequent increase in cell proliferation (Takahashi et al., 1998). In addition, it has been shown that exposure to TGF- $\beta$  results in increased MIF expression in a colon cancer cell line (Meyer-Siegler et al., 2006). Furthermore, other investigators observed an increase in the level of cytotoxic T lymphocytes following MIF inhibition achieved by using specific antibodies, and the number of apoptotic tumor cells increased following MIF inhibition (Abe et al., 2001). Tumors arising in the MIF-knockdown cells grew less rapidly and also showed an increased degree of apoptosis (Hagemann et al., 2007). These findings, therefore, suggest that once keratinocytes acquire mutations by UVB-induced DNA damage, they may become malignant, and MIF may thus play a dual role in promoting the growth of these tumor cells and inhibiting their apoptosis.

4.3 MIF and UV-Induced skin inflammatory responses

UVB stimulates the production of several proinflammatory cytokines, including TNF- $\alpha$ , IL-1 and IL-6 in the skin, and these proinflammatory cytokines are considered to be closely related to the progression of skin carcinogenesis (Moore et al., 1999, Murphy et al., 2003, Kim et al., 2010). UVB-induced inflammatory responses, such as the production of cytokines and the infiltration of inflammatory cells, are clearly associated with the development of skin tumors. The inhibition of this inflammatory response via topical application of an anti-inflammatory drug inhibits the acute inflammatory responses after UVB exposure, and decreases tumor formation after chronic exposure (Wilgus et al., 2003). MIF plays a direct role in both inflammation and tumorigenesis (Bach et al., 2008). UVB exposure in MIF Tg mice resulted in greater leukocyte infiltration than in WT mouse skin (Honda et al., 2009). Moreover, UVB irradiation enhances the expression of MIF in the epidermis, and MIF Tg mice showed higher levels of MIF mRNA expression after UVB exposure (Shimizu, 1999c). Once released, MIF acts as a proinflammatory cytokine to induce the expression of other inflammatory cytokines, including IL-1, IL-6 and TNF- $\alpha$  (Toh et al., 2006, Sanchez-Zamora et al., 2010, Donnelly, 1997). Since the intense inflammation in the skin in response to UVB irradiation was found to correlate with the early onset of carcinogenesis and a higher incidence of tumors after chronic UVB exposure, this finding confirms the likely role of MIF in this process.

5. Conclusions

Chronic exposure to UV irradiation induces early-onset skin carcinogenesis, and many inflammatory cytokines are related to the induction and progression of UV-induced skin cancer (Table 1). Chronic UVB exposure enhances MIF production, which may inhibit the p53-dependent apoptotic processes, thereby inducing photocarcinogenesis in the skin (Figure 4). This newly identified mechanism may positively contribute to our overall understanding of photo-induced skin damage, which ultimately results in carcinogenesis.

Progression of carcinogen	cytokines	References
Modulation of UV-induced apoptosis	MIF	Honda <i>et al.</i> , 2009
		Martin <i>et al.</i> , 2009
	IL-12	Schwarz <i>et al.</i> , 2002
	IL-18	Schwarz <i>et al.</i> , 2006
Chronic inflammation	TNF- $\alpha$	Moore <i>et al.</i> , 1999
	IL-1	Murphy <i>et al.</i> , 2003
	IL-6	Kim <i>et al.</i> , 2010
	MIF	Honda <i>et al.</i> , 2009
Immunosuppression	IL-10	Salazar-Onfray <i>et al.</i> , 1999 Weiss <i>et al.</i> , 2004

Table 1. Skin cancer and related inflammatory cytokines



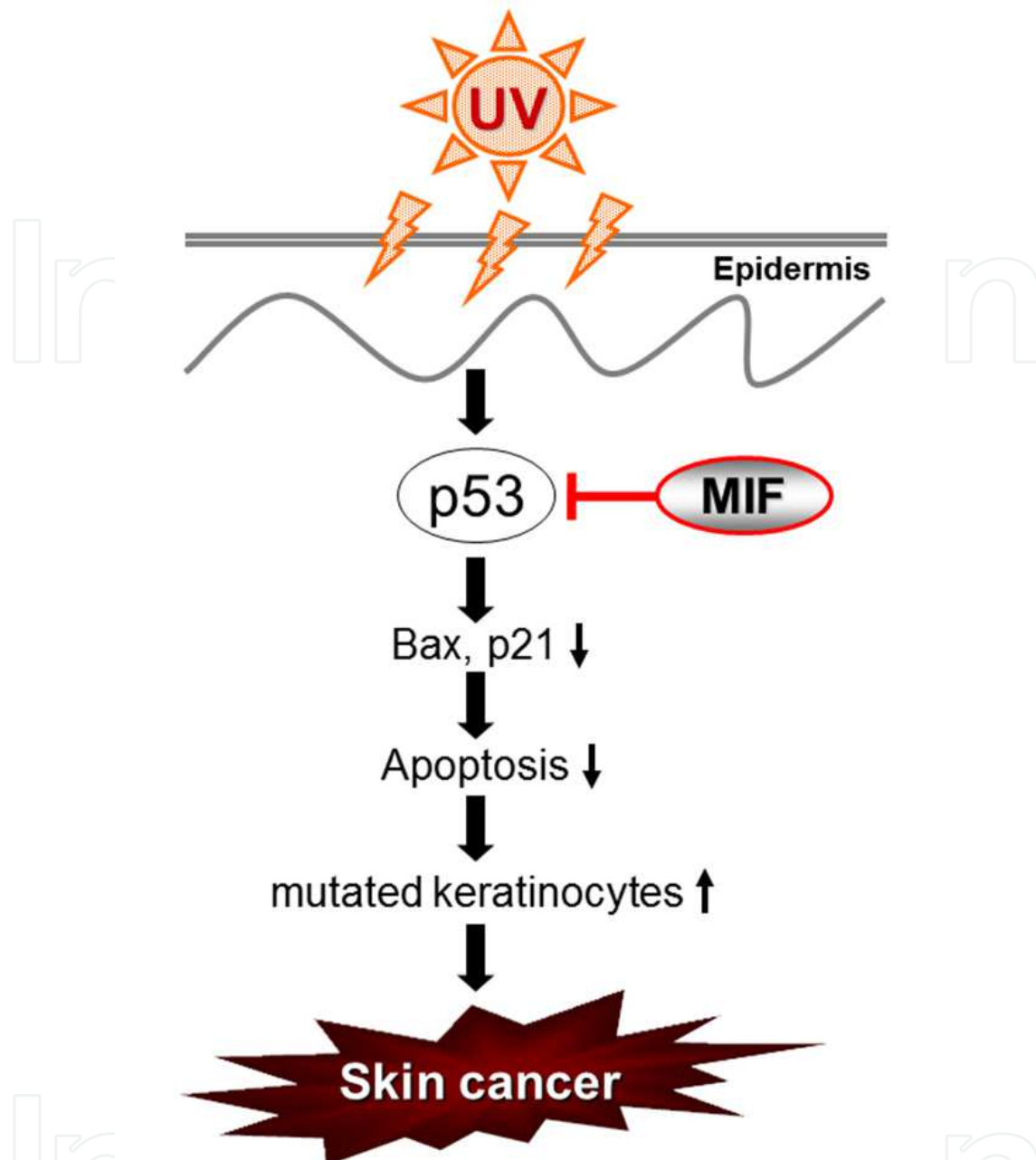


Fig. 4. MIF inhibits p53-dependent apoptotic processes. UVB exposure enhances MIF production, which may inhibit the p53-dependent apoptotic processes by blocking the relevant expression of apoptosis-regulatory genes, including those encoding p53, p21 and bax, thereby inducing photocarcinogenesis in the skin.

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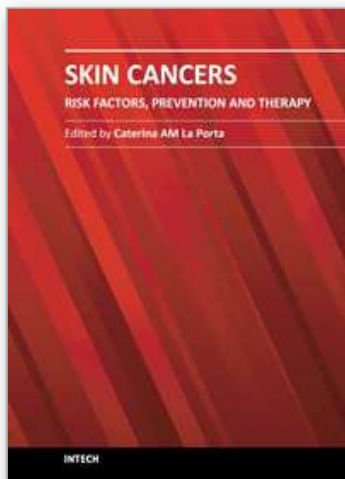
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## **Skin Cancers - Risk Factors, Prevention and Therapy**

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Skin cancers are the fastest growing type of cancer in the United States and represent the most commonly diagnosed malignancy, surpassing lung, breast, colorectal and prostate cancer. In Europe, the British Isles have been the highest rates of skin cancer in children and adolescents. The overall idea of this book is to provide the reader with up to date information on the possible tools to use for prevention, diagnosis and treatment of skin cancer. Three main issues are discussed: risk factors, new diagnostic tools for prevention and strategies for prevention and treatment of skin cancer using natural compounds or nano-particle drug delivery and photodynamic therapy.

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