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1 **Title: The Aryl hydrocarbon receptor pathway plays a central role in the**
2 **cutaneous response to pollutants**

3 **Short title: Skin response to pollutants and the AhR**

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25 Short- and long-term exposure to atmospheric pollution has significant health effects. The
26 skin is the organ directly in contact with pollutants and is responsible for protection of the
27 organism. Particulate matter (PM) such as polycyclic aromatic hydrocarbons (PAHs) are the
28 basis of certain pulmonary as well as dermatological complications. Pollution exacerbates
29 certain illnesses such as atopic dermatitis and cancer, and it may also participate in delaying
30 wound healing and in the occurrence of chronic ailments such as diabetes. The aryl
31 hydrocarbon receptor (AhR) transcription factor at the core of these responses to pollutants is
32 expressed by all cells of the skin. The AhR is subject to tight regulation that depends on its
33 ligand. Pollutants act in a deleterious manner via the AhR on the behavior of keratinocytes as
34 well as fibroblasts. Natural ligands, on the other hand, allow the noxious effects of pollution
35 to be countered. Modulation of AhR appears to be an excellent therapeutic target to improve
36 or stop the cutaneous problems linked to pollution.

37

38 **Keywords:** atopic dermatitis, pollution, skin, wound healing

39 **Introduction**

40
41 It is nowadays recognized that pollution is a major public health problem caused by an
42 increase in the prevalence of numerous cardiovascular, pulmonary, and dermatological
43 illnesses (1, 2). Atmospheric pollution is due to air contamination by different natural gases
44 derived from emissions by the vegetation as well as by soil erosion and of anthropomorphic
45 origin produced by human activities. These pollutants are classified into two distinct families:
46 primary pollutants and secondary pollutants, the latter undergoing modification by the
47 primary pollutants. Atmospheric pollution comprises gases such as carbon dioxide and sulfur
48 dioxide, as well as particulate matter (PM) emitted by various human activities. FPs contain
49 heavy metals and polycyclic aromatic hydrocarbons (PAHs). These components are produced
50 by road and air traffic as well as by cigarette smoke (3). Dioxins such as TCDD (2,3,7,8-
51 tétrachlorodibenzo-*p*-dioxin) are derived mainly from wood stoves and forest fires; they are
52 part of the family of PAHs. Exposure to pollutants particularly affects the skin, which is an
53 organ in direct contact with the pollution. For example, toxic and cancerogenic dioxins
54 readily penetrate the skin due to their lipophilic properties (4). On the other hand, pollutants
55 reach the lungs by respiration, and their passage in the blood flow can affect other organs
56 such as the skin (4). A link between pollution and chronic cutaneous inflammatory diseases
57 such as atopic dermatitis (AD) or impaired wound healing has recently been reported (5).
58 Similarly, it has been shown that long-term exposure to pollutants is associated with an
59 enhanced incidence of lung as well as skin cancers (6). The aryl hydrocarbon receptor (AhR)
60 transcription factor, which is expressed in all cutaneous cells, is central to all of these
61 pathophysiological processes (7, 8). The AhR signaling pathway is induced by PM in
62 particular, which have a high affinity for this receptor (7).

63 In light of the increasing concerns arising from pollution, there is ample merit in gaining a
64 better understanding of the consequences of pollution at the level of the skin in response to

65 the AhR. We here document the effects and the interactions that occur in skin in response to
66 pollution and that involve the AhR.

67 **1. Biology of the AhR**

68
69 The skin is the largest organ of the human body. It protects the organism from exterior
70 insults, and it plays a role as a sensor of the environment. This is why the cutaneous
71 homeostasis and the integrity of the skin need to be tightly regulated.

72 The AhR is expressed in all of the organs that act as barriers, such as liver, lungs, intestine,
73 and skin (7). The AhR is a helix-loop-helix domain transcription factor that responds to
74 endogenous and exogenous signals, and it is, therefore, also able to modulate these effects. It
75 is found in the cytoplasm of all cutaneous cells, both in the epidermis and the dermis, and it is
76 essential for homeostasis of the skin (7).

77 The AhR is activated in the cytoplasm after binding of its ligand, which allows induction of
78 the signal for its translocation to the nucleus. Thanks to chaperone proteins, the AhR is
79 directed to the nuclear compartment where it heterodimerizes with the molecule ARNT (Aryl
80 hydrocarbon Receptor Nuclear Translocator). This protein complex is able to activate the
81 transcription of certain genes, by binding to their XRE (Xenobiotic Response Element)
82 promotor regions (**Figure 1**). On the other hand, the AhR activates the expression of its own
83 AhRR (Aryl hydrocarbon Receptor Repressor) repressor, thereby ensuring a negative
84 feedback loop. AhRR binds to ARNT in the nucleus and prevents the binding and the action
85 of the AhR/ARNT complex (7).

86

87 **1.1. Nature of the AhR ligands**

88 Numerous ligands are capable of activating the AhR pathway. They are classified into three
89 groups according to their nature.

90

91 **1.1.1. Endogenous ligands**

92 UVB radiation is capable of generating dimers of tryptophan, called FICZ (6-
93 formylindolo[3,2-b]carbazole), which can bind to the AhR (9). These are referred to as
94 endogenous ligands. Activation of the AhR pathway by FICZ promotes pigmentation and
95 hence improves protection of the DNA. Due to this, the AhR is sensitive to the environment
96 and it acts as a sensor of UV radiation (7). When exposed to UVB radiation, mice lacking the
97 AhR exhibit less cutaneous pigmentation than wild-type mice (10).

98 **1.1.2. Natural exogenous ligands**

99 The AhR can bind with high affinity to ligands in food. Phytochemical antioxidants such as
100 flavonoids, which are responsible for the color of fruits and plants, or glucosinolates that give
101 rise to the bitterness of mustard and cauliflower, are exogenous natural ligands of the AhR.
102 Their binding induces translocation of the nuclear factor Nrf2 to the nucleus, allowing
103 expression of antioxidant enzymes such as Nqo1 (Quinone oxidoreductase) and oxygenase-1
104 (HO-1) (11-13) that protect cells from damage generated by ROS. A recent study has shown
105 that these exogenous natural ligands exert a barrier function by regulating transepidermal
106 water loss (14).

107 **1.1.3. Synthetic exogenous ligands**

108 Lastly, particulates from pollution, such as PAHs or TCDD, are synthetic exogenous ligands
109 with very high affinities. Their binding to the AhR promotes the generation of reactive
110 oxygen species, which are known to cause DNA damage. Pollution gives rise to an increase
111 in inflammation and it exacerbates cutaneous inflammatory diseases such as atopic dermatitis
112 as well as psoriasis (15).

113 The nature of the ligand determines the AhR response. In humans, the specificity of the
114 binding of the AhR depends on a valine residue situated at position 381. In case of

115 substitution by an alanine, the specificity increases, unlike substitution by an asparagine,
116 which leads to abolition of the binding.

117

118 **2. Consequences of the activation of the AhR at the cutaneous level**

119 The epidermis is the most superficial layer of the skin. It is mainly composed of keratinocytes
120 that become differentiated from the basal layer to the corneal layer. There are also
121 melanocytes, which are responsible for pigmentation of the skin. The epidermis plays an
122 essential role in the barrier function. It is sensitive and in direct contact with environmental
123 particulates, particularly those found in pollution. The underlying dermis is also highly
124 exposed. Park *et al.* exposed dermal fibroblasts to particulate pollution for 24 h, and they
125 identified 1977 genes for which the expression was altered. We report here the consequences
126 of this substantial transcriptional modification on certain cutaneous functionalities.

127

128 **2.1. Loss of the barrier function of the skin**

129 It has been shown that reconstructed human epidermis exposed long-term to tobacco smoke
130 undergoes histological changes. The spinous and granular layers were no longer visible,
131 while the thickness of the corneal layer was increased (3). Another experiment performed on
132 cultured keratinocytes reported an increase in the differentiation of the cells in response to
133 TCDD (16). The development of the corneal layer at the expense of the granular and spinous
134 layers can be explained by acceleration of the differentiation of the keratinocytes (3). By
135 contrast, the ligand FICZ is capable of decreasing the thickness of the epidermis and of
136 improving the transepidermal loss of water in mice with atopic dermatitis (17). On the other
137 hand, mice that specifically lack the AhR in keratinocytes (K5AhR-KO) exhibited greater
138 transepidermal water loss than the wild type mice (18). The AhR also targets the expression
139 of filaggrin, *FLG*, which is essential for the barrier function of the skin by participation in the

140 formation of the corneal layer. Mice lacking the AhR (AhR KO) express lower levels of
141 genes associated with the barrier function (14). The expression of filaggrin, occludin, and
142 involucrin increase following mechanical stress in healthy mice, but this increased expression
143 is not seen in mice lacking the AhR. The loss of AhR appears to result in less cutaneous
144 resistance to mechanical stress. Moreover, the expression of genes coding for extracellular
145 matrix anchoring proteins (collagens IV and VII) and the expression of genes coding for
146 proteins involved in cell-cell junctions (corneodesmosin, desmocollin-1, and desmoglein-1)
147 were found to be decreased in a reconstructed epidermis model after exposure to cigarette
148 smoke (3). This led to a decrease in the efficacy of the epidermal barrier by the loss of cell
149 cohesion. The AhR is, therefore, subject to very tight regulation at the level of the epidermis.
150 Depending on the ligand and the context, the AhR can maintain or change the homeostasis of
151 the epidermis.

152

153 **2.2. Modulation of the proliferative and the migratory capacities of cutaneous cells**

154 The AhR also participates in the activation of growth factors such as EGF (epidermal growth
155 factor) involved in cell differentiation or proliferation. AhR KO mice exhibit faster dorsal
156 wound healing than normal mice, In this model, the re-epithelialization is faster due to faster
157 keratinocyte migration. There are more fibroblasts, and the collagen level is higher at the
158 level of the granulation tissue. Fibroblasts secrete high levels of active TGF- β (transforming
159 growth factor), which participates in enhancing wound healing (18). This study shows that
160 decreasing in AhR activity could be a new potential way to treat chronic lesions. By contrast,
161 activation of the AhR by PAHs results in a decrease in proliferation as well as entry into
162 apoptosis of keratinocytes and fibroblasts, which could participate in impaired healing (19).

163

164

165 **2.3. Modulation of MMPs**

166 Matrix metalloproteinases (MMP) induce changes in the quantity and the structure of
167 collagens. A model of reconstructed human skin, and *Hairless* *-/-* mice, exposed to tobacco
168 smoke were shown to exhibit a significant increase in MMP-1 and MMP-3 (3). These
169 proteins are responsible for the degradation of type I, II, and III collagen and type IV and V
170 collagen, respectively. On the other hand, the expression of inhibitors of MMPs, TIMP-1 and
171 TIMP-3, is not altered in cutaneous tissue. Tobacco smoke and pollutants alter the balance
172 between the biosynthesis and the degradation of collagen. The balance tends toward
173 degradation of collagen in favor of the induction of MMPs.

174 It was recently shown that the active form of TGF- β is an essential factor in homeostasis of
175 the epidermis and growth of the dermis. Tobacco smoke, as well as PAHs, induce the non-
176 functional form of TGF- β , thereby leading to a reduction in the biosynthesis of extracellular
177 matrix proteins (20). Similarly, tobacco smoke can result in oxidative stress by the induction
178 of reactive oxygen species (ROS) in fibroblasts. ROS can then induce damage at the level of
179 the DNA and stimulate the production of MMPs. The AhR is a transcription factor activated
180 in response to pollutants, thereby giving rise to changes at the level of the skin. The activation
181 of these transcription factors thereby leads to oxidative biological responses such as the
182 formation of ROS (3) and it can also directly activate the production of MMP-1 and MMP-3,
183 which are responsible for the degradation of collagen and elastin fibers (21).

184 The AhR pathway activated by the components of tobacco smoke and pollutants plays a
185 central role in the process of extrinsic aging as a result of pronounced alterations at the level
186 of the dermis.

187

188

189

190 **2.4.Loss of the viscoelasticity**

191 *In vivo* studies in mice and of cultured fibroblasts that have been exposed to tobacco smoke
192 or to atmospheric pollutants have revealed changes in the biosynthesis of type III, IV, and VII
193 collagens as well as elastin fibers (5). These changes translate into a significant decrease in
194 the matrix components in the dermis and neosynthesis of abnormal elastin (22). Such
195 dysmorphic elastic fibers can lead to elastosis or changes that lead to a loss of the
196 viscoelasticity of the skin. Thus, these alterations appear to be responsible for the formation
197 of wrinkles and hence early extrinsic aging.

198 On the other hand, the damaged skin of mice exposed to tobacco smoke exhibits a higher
199 level of elastase than non-exposed mice. The elastic fibers are then degraded more, thereby
200 perturbing the plasticity of the wound (23).

201

202 **2.5. Hyperpigmentation**

203 Recent studies have indicated that photoprotection by tanning can occur in the absence of UV
204 radiation. Treatment of melanocytes with oligonucleotides such as the 7-mer
205 pApGpTpApTpGpA is able to induce tyrosinase activity and stimulate the synthesis of
206 melanin in the absence of UV light (24). Other studies have shown that ligands of the AhR,
207 such as dioxin or PAHs, induce the proliferation of melanocytes (8). This mechanism can,
208 therefore, provide scientific proof of the association between spots of pigmentation and
209 exposure to FPs. Similarly, the exposure of primary melanocytes cultures to atmospheric
210 particulates induces transcriptional expression of genes involved in the formation of skin
211 spots (4). Lastly, activation of the AhR pathway in melanocytes in response to pollutants
212 induces cell proliferation and high levels of melanin synthesis, leading to the appearance of
213 pigment spots on the skin.

214

215 **2.6. Inflammation**

216 There AhR does not result in specific immune responses, due to the fact that the AhR is
217 present in several types of immune cells and because the response differs depending on the
218 bound ligand. The AhR can also activate the expression of pro-inflammatory or
219 immunosuppressive cytokines such as interleukin (IL-) 1 β (IL-1 β) or TGF- β in
220 keratinocytes. It has been shown that the AhR increases the expression of a pro-inflammatory
221 cytokine, IL-8, in keratinocytes in a manner dependent on a response to oxidative stress
222 induced by benzo[a]pyrene (BaP) in cigarette smoke (25). Exposure of a reconstructed
223 epidermis to cigarette smoke induced a high degree of inflammation of the skin by the
224 expression of IL-1 α , IL-8, and IL-18 (3). Keratinocytes treated with PAHs exhibited an
225 increase in IL-1 α and IL-1 β , which are interleukins that also perturb the dermis. Co-culture of
226 these keratinocytes with fibroblasts revealed expression of MMP1 and COX-2 in dermal cells
227 (26). In 2005, Masafumi Tauchi and their team generated transgenic mice that constitutively
228 express the AhR in keratinocytes, under the control of the K promoter (27). The receptor is
229 active in the complete absence of ligands, the aim, therefore, being to activate the
230 transcription of target genes without a chemical entity (AhR ligands). These mice exhibited
231 cutaneous inflammatory lesions and pronounced itching, and molecular analysis by
232 microarrays revealed overexpression of pro-inflammatory genes. Non-immune cells are able
233 to produce TNF alpha and IL-8 after activation of the Toll-like receptor 2 (TLR-2) (28). Hou
234 *et al.* showed that TCDD increases the secretion of TNF alpha and IL-8 after induction of
235 TLR-2. Suppression of the AhR by KO blocks the production of these pro-inflammatory
236 cytokines (28).

237 The AhR hence plays a central role in the regulation of cutaneous inflammation, and its
238 activation results in skin lesions.

239

240 **3. Link with cutaneous pathologies**

241 **3.1. Atopic dermatitis**

242 Activation of the AhR by pollutants appears to be correlated with chronic inflammatory
243 diseases such as atopic dermatitis (AD). AD is a skin disease that occurs mainly in childhood.
244 It results in several clinical signs such as itching, erythema, and chronic xerosis. At the
245 molecular level, the barrier function of the skin is altered due to, in certain cases, a loss of
246 function of the gene coding for filaggrin. It was not until very recently that atmospheric
247 particulates have been taken into account in the development and the exacerbation of the
248 symptoms of AD. There is a correlation between the severity of AD in children and outdoor
249 as well as indoor pollution such as particles present in paint (29). On the other hand, the
250 expression of the AhR and ARNT are increased in the lesions of patients with AD relative to
251 healthy skin (15).

252 A recent study used an AhR-CA mouse model that mimics AD. The keratinocytes of these
253 mice constitutively express the AhR. This cytoplasmic receptor is, therefore, a key factor in
254 AD (30).

255 In the presence of PAHs, AhR-CA mice overexpress the gene Artemin (*Artn*), which is a
256 target of the AhR transcription factor, in the keratinocytes. The artemin protein (ARTN) is
257 upregulated in the keratinocytes and is responsible for hyperinnervation and an increase in
258 pruritis. The skin is, therefore, hypersensitive and the itchiness is exacerbated, in the same
259 study, it was shown that the AhR is activated in DA lesions in humans (30). Moreover, it has
260 been shown that *in vitro* exposure of human keratinocytes to pollutants leads to increased
261 expression of ARTN (30). Hu *et al.* have shown that the level of AhR in the serum of AD
262 patients is higher than that of healthy individuals. The expression of AhR mRNA is positively
263 correlated with the severity of the disease as well as to the level of IL-6 present in the serum
264 of AD patients (31).

265 **3.2. Impaired wound healing**

266 One of the main complications of diabetic patients is a lack of substantial wound healing,
267 resulting in acute chronic lesions. It has been shown that smoking increases the risk of foot
268 amputation in diabetic patients (32). Cigarette smoke is a direct activator of the AhR pathway
269 as it contains more than 3800 components, including PAH (21). A number of clinical and
270 experimental studies have shown the impact of cigarette smoke on chronic wound healing
271 (33-35). Sorensen *et al.* made cutaneous excisions of smokers and non-smokers, and analysis
272 of the lesions revealed perturbed inflammation and a decrease in the proliferation of
273 fibroblasts that could participate in a delay of wound healing (35). Michaud *et al.* indicated
274 that extracts of cigarette smoke inhibited vascular endothelial growth factor (VEGF), which
275 perturbed the migration and the formation of capillaries formed by HUVECs (human
276 umbilical vascular endothelial cells) (37). These studies suggest that for diabetic patients,
277 evaluation of tobacco dependency and stopping smoking are key to improving chronic wound
278 healing. Indeed, cessation of smoking of more than three weeks preoperatively reduced
279 impaired wound healing after surgery (36).

280 The cutaneous vascular density and blood flow are decreased with aging or pathologies such
281 as diabetes, or in the presence of chronic lesions, thereby increasing the expression of
282 hypoxia-inducible factor 1 α (HIF-1 α) in tissues, which allows expression of angiogenic
283 genes. Several studies have shown that the loss of HIF-1 α subunits in the endothelium leads
284 to vascular anomalies. Under limiting oxygen concentrations, HIF-1 α is stabilized, which
285 allows it to be translocated to the nucleus where it binds to ARNT, like AhR. The HIF-
286 1 α :ARNT heterodimer binds to hypoxia response elements (HRE) in target genes inducible
287 by hypoxia (37, 38). It has been shown that in the presence of pollutants such as PCB126,
288 hypoxia significantly interferes with the functions of the AhR, which could negatively affect
289 CYP1A1 mRNA expression, resulting in a lower protein level and hence less enzymatic

290 activity (39). This negative interaction between the AhR and hypoxia signaling pathways
291 appears to depend at least in part on the availability of ARNT. Furthermore, it has been
292 shown that ARNT KO mice exhibit vascular and angiogenic impairments that can contribute
293 to impaired migration of immune cells during the first stages of wound healing (40). This
294 negative interaction has been observed in liver (41, 42) and, unlike the study of Pollenz *et al.*
295 on the induction of the AhR by TCDD, does not indicate competition for ARNT under
296 hypoxic conditions (43).

297 Thus, the presence of tissue hypoxia can significantly perturb the normal transcriptional
298 response of the AhR after exposure to PCB 126, which could ultimately affect cell
299 metabolism and contribute to the development of chronic lesions as a result of major
300 cutaneous vascular defects. Moreover, cigarette smoke has adverse effects on vascular
301 biology, inducing endothelial dysfunction and arterial stiffness (44). Cigarette smoke causes
302 defective angiogenesis that can be linked to a lack of VEGF (45), a main pro-angiogenic
303 factor for which the expression depends on HIF-1 α (46, 47). More extensive studies focused
304 on skin and impaired wound healing in this toxic context of pollutants are necessary to
305 improve the understanding of these multiple interactions.

306
307

307 **3.3. Cancer**

308 Long-term exposure to indoor and outdoor air pollution is associated with an increased
309 incidence of cancer, particularly lung cancer (6). PAHs exhibit cancerogenic properties by the
310 formation of DNA adducts following the activation of cytochrome P450, which leads to the
311 formation of diol-epoxide metabolites (48). Matsumoto and his team have shown that
312 repeated topical application of PAHs on the back of AhR $+/+$ mice led to the formation of
313 epidermoid carcinomas after 29 weeks, unlike AhR $-/-$ mice (49). The formation of cutaneous
314 tumors in the AhR $+/+$ mice was mediated by the expression of CYP1A1, induced by extracts
315 of air pollution particles (49). The AhR plays a major role in the cutaneous carcinogenesis

316 induced by PAHs. The epithelial–mesenchymal transition (EMT) results in invasive cancers
317 by the formation of metastasis, and it is known that Slug is a key transcription factor in the
318 EMT. It inhibits the proteins required for cell-cell interaction, such as E-cadherins, and it
319 allows cell migration. There are several XRE regions in the Slug gene promoter, to which the
320 AhR can bind. Inhibition of the AhR leads to suppression of the expression of Slug (50).
321 Prolonged exposure to different pollutants can lead to certain cancers becoming more
322 aggressive due to an increased metastatic potential.

323

324 **4. Conclusion/perspectives**

325 The AhR is subjected to extremely tight regulation. Ligands of a synthetic exogenous nature,
326 such as pollutants, can disrupt this balance. In a context of pollution, the AhR promotes the
327 generation of ROS, which cause DNA mutations. Reactive oxygen species promote the
328 secretion of pro-inflammatory cytokines and decrease the expression of filaggrin by the
329 NFκB and AP1 pathways. The proliferation of melanocytes and melanogenesis are enhanced
330 in the presence of pollutants. Lastly, at the level of the dermis, activation of the AhR by
331 synthetic exogenous ligands generates ROS and the activity of metalloproteases is increased.
332 Fibroblasts synthesize an abnormal form of elastin and an inactive form of TGF-β. Activation
333 of the AhR by pollutants also leads to the formation of cutaneous tumors and it can promote
334 the formation of metastasis.

335 The structure and the composition of the skin are modified in the presence of pollutants. The
336 extracellular matrix is degraded, inflammation is increased, and pigmentation is stimulated.
337 These changes are directly linked with early cutaneous aging, serious forms of AD, delayed
338 wound healing, and the formation of cancer (**Figure 2**). Hidaka and their team have shown
339 that the Artemin gene is a target of the AhR, inducing substantial pruritis in the presence of

340 PAH in mice. Inhibition of *Artemin* reduces the symptoms of AD (30). In humans, this gene
341 is found in AD lesions, Strong activation of *Artemin* in response to pollutants is, therefore,
342 possible. *Artemin* could also be a therapeutic target in AD. Interestingly, Van Den Bogaard *et*
343 *al.* were the first to show a beneficial therapeutic effect of activation of the AhR on the
344 barrier function of the skin by coal tar. The expression of filaggrin was restored in the
345 keratinocytes of the reconstructed epidermis of AD patients with a heterozygous mutation
346 (FLG^{-/+}) (51). In 2020, Furue, assigned the beneficial effects of natural or medicinal ligands
347 of the AhR to anti-oxidant properties via activation of NRF2 in AD patients (52). The
348 AhR/NRF2 pathway is, therefore, a potential therapeutic target for AD patients.

349 Food items can provide flavonoids that can compete with pollutants by exerting an anti-
350 oxidative role (8). Haas and their team have shown that suppression of the AhR ligands in the
351 food of mice decreased the barrier function similar to mice lacking the AhR. After being fed
352 a diet enriched in I3C (indole-3-carbinol), these mice fully recovered their barrier function
353 (14). Recently, studies have shown that a flavonoid, eupapholin, can attenuate the oxidative
354 stress and inflammation induced in cultured keratinocytes by fine particulates (53).
355 Eupapholin appears to reduce the generation of ROS and the activity of the MAP Kinase
356 pathway, which is the basis for NFκB activation (54). Other than environmental or personal
357 actions to reduce pollutants, one can imagine counteracting the effects of pollution by a
358 specific diet that results in high levels of natural exogenous ligands of the AhR to limit the
359 action of pollutants.

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505 **Figure legends:**

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507 **Figure 1. Signaling by the AhR in response to its ligand.**

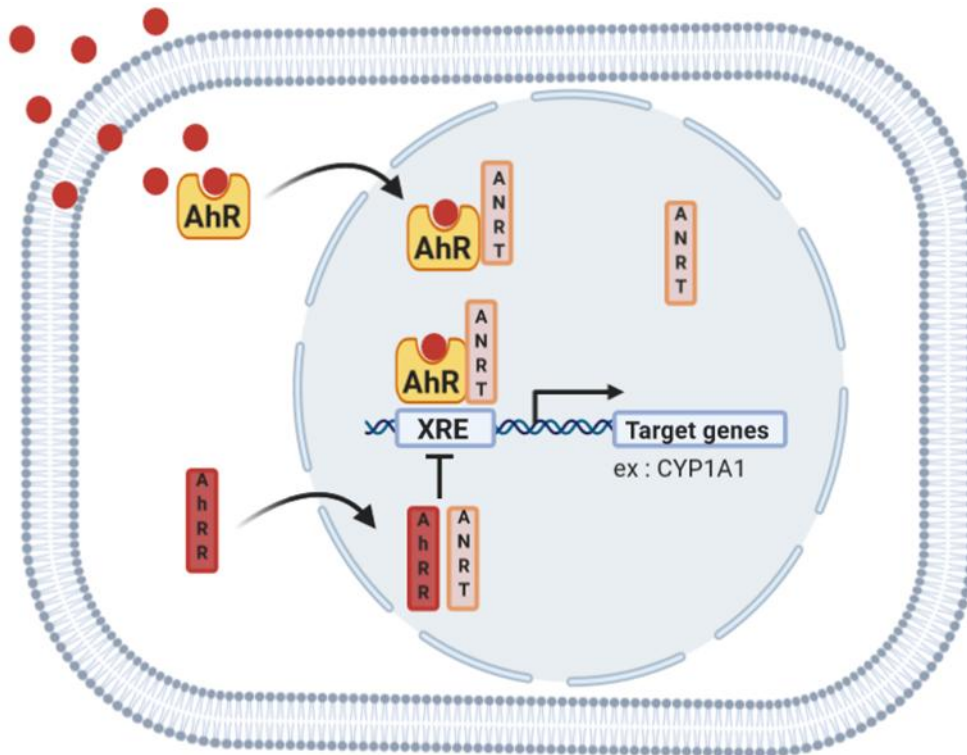
508 AhR: Aryl hydrocarbon Receptor; ARNT: Aryl hydrocarbon Receptor Nuclear Translocator; XRE:
509 Xenobiotic Response Element; AhRR: Aryl hydrocarbon Receptor Repressor. In the cytoplasm, the
510 AhR binds its ligand and is then transported to the nucleus. In the nucleus, the AhR and its ligand
511 heterodimerize with the ARNT to bind to the XRE in promoter regions of target genes such as, for
512 example, cytochrome P450 1A1 (CYP1A1) (55).

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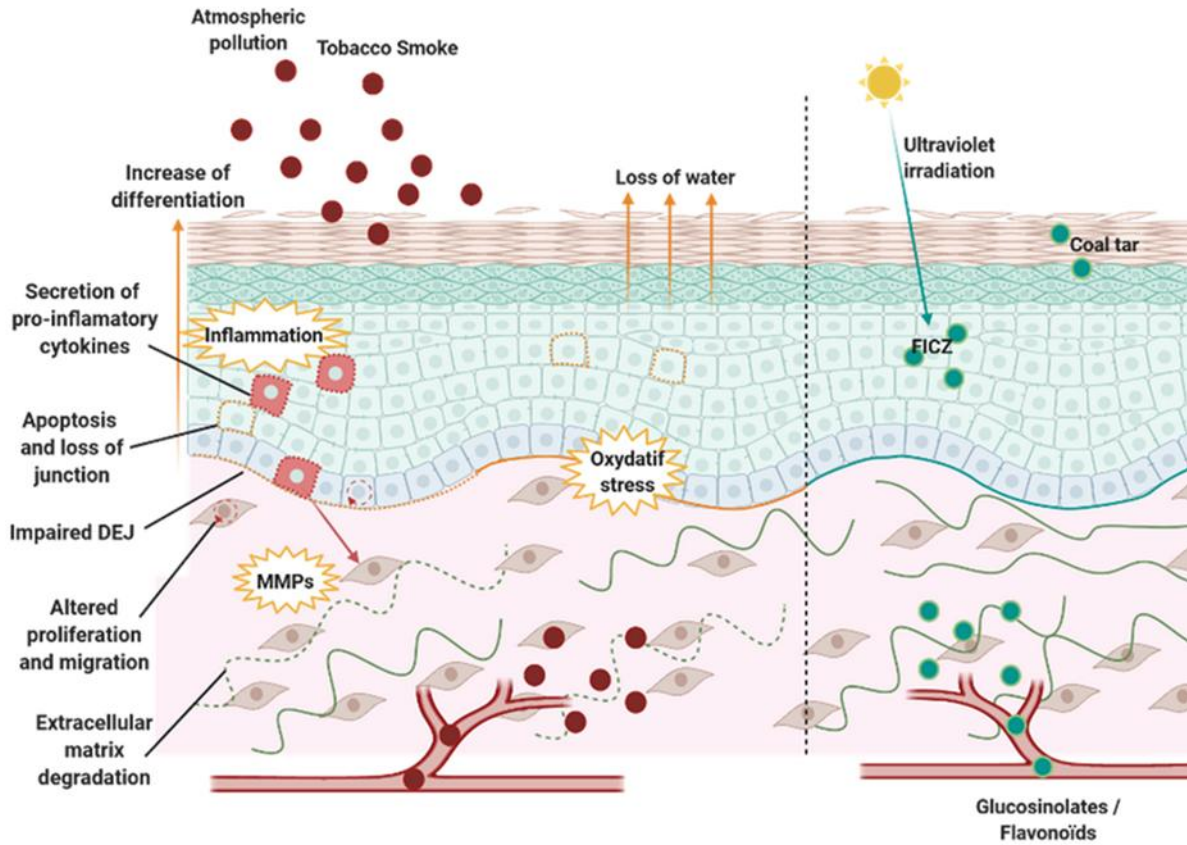
514 **Figure 2. Impact of pollution on the cutaneous functionality involving the AhR.**

515 Pollution and cigarette smoke are composed of numerous ligands capable of activating the AhR.
516 Oxidative stress induced by pollution perturbs the overall balance of the skin. This results in
517 inflammation of the epidermis by the secretion of pro-inflammatory cytokines (1), greater trans-
518 epidermal water loss (2) due to the loss of intercellular junctions (3), and destabilization of the
519 dermal-epidermal junction (DEJ) (4). The keratinocytes of the basal layer lose their capacity for
520 proliferation and their differentiation is increased, thereby enhancing the supra-basal layers (5). The
521 proliferation and the migration of fibroblasts are altered (6), which can lead to impaired wound
522 healing. Within the derma, the extracellular matrix is degraded (7) by the presence of
523 metalloproteases (MMPs) induced by the inflamed keratinocytes in particular. However, endogenous
524 or exogenous natural entities are capable of counteracting the adverse effects of pollution (8).

525 **Figures :**
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528 **Figure 1. Signaling by the AhR in response to its ligand.**
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Figure 2. Impact of pollution on the cutaneous functionality involving the AhR.