



Could *Malassezia* yeasts be implicated in skin carcinogenesis through the production of aryl-hydrocarbon receptor ligands?

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ABSTRACT

Malassezia yeasts are found on the skin of all humans and many warm-blooded animals. *In vitro* they have the ability to synthesize potent ligands (indolo[3,2-b]carbazole, malassezin and indirubin) of the aryl-hydrocarbon receptor (AhR; synonym: dioxin receptor) when the sweat contained L-tryptophan is used as the single nitrogen source. The production of these AhR-ligands has been associated with pathogenic strains of a certain *Malassezia* species (*Malassezia furfur*) but recent evidence shows that this property is widely distributed in almost all currently known *Malassezia* species. AhR is associated with carcinogenesis and the potential connection of these ubiquitous skin symbionts, and putative pathogens, with skin neoplasia should be evaluated mainly focusing on mechanisms related to the distinctive ability of the yeast to produce potent AhR ligands.

Hypothesis: Synthesis of available pertinent data show a possible link between *Malassezia* produced AhR ligands and skin carcinogenesis, particularly of basal cell carcinoma (BCC).

BCCs are almost exclusively observed in animal species colonized by *Malassezia*. In humans and animals there is overlapping in the skin regions colonized by this yeast and affected by BCC. The potent AhR ligands synthesized by pathogenic *Malassezia* strains could contribute to tumor promotion by: modification of the UV radiation carcinogenesis, alterations in the salvage/survival of initiated tumor cells, inhibition of cell senescence, interaction with vitamin D metabolism, promotion of immune tolerance and finally pro-carcinogenic modulation of cell cycle progression and apoptosis.

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Introduction

The *Malassezia* genus currently includes 13 species [1,2] and yeasts of this genus are found on the skin of all humans and many warm blooded animals [1,2]. In humans the most commonly isolated species are *Malassezia globosa*, *Malassezia restricta*, *Malassezia sympodialis* and *Malassezia furfur* [3,4]. These species are strictly lipophilic and depend on skin lipids for survival. Additionally, they are capable of producing an extensive array of bioactive indolic compounds *in vitro* when L-tryptophan is used as the single nitrogen source in their medium [5], including some of the most potent activators of the Aryl Hydrocarbon Receptor (AhR), like indolo[3,2-b]carbazole (ICZ) and indirubin [6–9]. Although the synthesis of these compounds was originally associated with pathogenic *M. furfur* strains isolated from the skin of patients with seborrheic dermatitis, pityriasis versicolor or dandruff [6,7], it becomes increasingly evident that all known *Malassezia* species possess

the ability to synthesize these compounds under certain environmental conditions and activate the AhR *in vitro* [8–10].

Malassezia yeasts are implicated in the pathogenesis of pityriasis versicolor [11] and seborrheic dermatitis [12] yet, as recent clinical data imply, they also participate to the aggravation of certain clinical subtypes of atopic dermatitis [12,13] and psoriasis [14]. The contribution of *Malassezia* to the pathogenesis of the aforementioned immune mediated diseases points to a vivid interaction of this yeast with the host's skin immune system. However, for reasons that are currently poorly understood, the individual immunologic response to *Malassezia* yeasts may be quite variable in humans, ranging from usually absent or minimal stimulation in pityriasis versicolor [11,15] to significant inflammatory reactions in seborrheic dermatitis [12,16]. Yeast and host factors seem to contribute to this variability. It has been proposed that certain indolic compounds produced in the lesions of pityriasis versicolor by *Malassezia* yeasts are responsible for alterations in melanocyte function [17] and for the absence of signs of inflammation [15], both prominent clinical characteristics of this skin condition. Yet, *M. furfur* strains isolated from strongly inflammatory lesions of seborrheic dermatitis are characterized by the ability to synthesize

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increased quantities of different indolic compounds *in vitro* [6]. The increased prevalence of seborrheic dermatitis among immunosuppressed individuals like transplant recipients [18] or HIV patients [16], also highlights the decisive role of the patients' immune system in the population control of the *Malassezia* yeasts [19].

Basal cell carcinoma (BCC) of the skin is the malignant tumor with the highest incidence among Caucasians worldwide. Solar ultraviolet radiation (UVR) is the most important carcinogen for this tumor, yet not all BCCs can be attributed to ambient UVR since not only many tumors arise on relatively sun protected skin localizations but they are also rare at certain areas subjected to intense UVR exposure throughout life, like the dorsal aspects of the hands [20,21]. Regarding the pathogenesis of BCC recent data mainly implicate activating mutations of the hedgehog pathway at the cellular level [21–23] as well as induction of immune tolerance locally by the establishing tumor [24,25] at the tissue level [26] (immunosubversion), a well recognized common process in the progression of many cancer types.

The AhR is an orphan receptor that in the adult mediates the metabolism of xenobiotics through induction of detoxifying enzymes. CYP1A1 activity is routinely used to assess the level of AhR activation [27]. AhR is a member of the Per-Arnt-Sim superfamily of transcription factors and functions as a key mediator of diverse chemical and physical environmental cues to the cell including food-originating mutagens, polycyclic aromatic and polyhalogenated aromatic hydrocarbons [28] as well as of the UVR according to more recent evidence [29,30]. In the absence of a ligand, AhR is located in the cytoplasm as part of a multimolecular regulatory protein complex [28]. Ligand binding induces a complex signaling to both nuclear and cell membrane downstream targets, where different member proteins of the complex are simultaneously involved. Upon destabilization of the regulatory complex AhR itself is translocated from the cytosol to the nucleus, where after heterodimerization with ARNT binds to specific response elements within the promoter region of target genes and modifies their transcription [28,31,32]. The AhR is widely known as the dioxin receptor because dioxin mediates its devastating effects through a sustained activation of this receptor and skin lesions, particularly in the form of chloracne are the most consistent symptom of adult dioxin intoxication [33]. However, besides the aforementioned toxicological events that underscore the role of AhR in epidermal metabolism, recent evidence indicates that AhR mediates a wide spectrum of important prenatal and postnatal functions in skin homeostasis, as slow metabolized AhR ligands are able to modify the differentiation of keratinocytes *in vitro* [34] and accelerate terminal skin development in mouse upon exposure *in utero* [35]. Moreover, in the adult skin AhR has pluripotent functions as it regulates aspects of the immune response [36], the cell cycle [37,38] and, as already mentioned, it also mediates part of the UVR induced cell alterations [29,30]. In human epidermis AhR and ARNT are expressed in a differentiation-dependent manner that establishes an expression gradient in parallel to the level of keratinocyte differentiation [39]. Therefore, as the production of potent AhR ligands in biologically significant amounts can happen during the metabolism of *Malassezia* yeasts on the skin, this receptor could play a central role in the ecological 'cross-talk' of *Malassezia* yeasts with cellular components in the upper part of the epidermis and the hair infundibulum. Long-term effects of this interspecies 'communication' to either the yeast or its host have not been investigated to date.

Hypothesis

Malassezia yeasts colonize human skin shortly after birth and reside on it throughout life. *Malassezia*-produced AhR ligands acti-

vate this receptor in HaCaT cells either in the form of culture extracts or as pure substances i.e. indirubin, ICZ, malassezin [8,9] and this could also happen in the skin through the continuous or intermittent production of the particular potent AhR ligands by the resident *Malassezia* yeasts. AhR activation has been recently shown to promote carcinogenesis in the skin of mice [40]. Moreover, earlier studies have also implicated polymorphisms of the AhR-dependent detoxifying enzymes, such as the CYP enzymes and glutathione-S-transferase (GST) in the pathogenesis of BCC [41,42]. Hence, we suggest that *Malassezia*-produced AhR ligands could act as skin carcinogens, especially for BCC. The suggested *Malassezia*-associated skin carcinogenesis is supported by: (a) the spatial relationship of the ecological niches of the *Malassezia* population on the body surface and the anatomical distribution of BCC on the skin, as well as the epidemiological evidence that link BCC prevalence to that of *Malassezia*-associated skin diseases. (b) The current pathobiological data, which infer an AhR mediated link between *Malassezia* yeasts and skin BCCs at cellular and tissue level. Based on the data presented below, we propose the hypothesis that *Malassezia*-induced modulations of the skin immune system and epidermal homeostasis could play a crucial role in BCC development and progression.

Discussion

Solar UV exposure is the most important single carcinogen for BCC, yet by far not every BCC can be attributed to sun exposure, and additional factors related to the host contribute substantially to the pathogenesis of many BCC cases [23]. Among host-dependent factors that have been linked to the occurrence of multiple BCCs on the same patient are polymorphisms in detoxifying enzymes [41,42]. The aforementioned non-homogeneous, partly UVR-independent anatomical distribution of these tumors is in line with the current hypothesis that carcinogenic factors acting *in loco* independently or in addition to UVR, may play a distinctive role in the pathogenesis of BCC. An appreciable locally modifying factor of skin carcinogenesis could be *Malassezia* yeasts which are characterized by a huge per species and per strain metabolic diversity and their niche is the hair infundibulum, corresponding to the presumptive origin of BCC [20–22]. This is further in line with the observed coincidence of BCC confluence and *Malassezia* colonization areas: both *Malassezia* and BCC are commonly found in some relatively UVR protected areas of the human face (i.e. eyelid, inner canthus, retroauricular area) as well as the 'seborrheic area' of the trunk [20]. Epidemiological observations that indirectly link *Malassezia* to BCC come from the study of patients with Parkinson's disease, in whom seborrheic dermatitis and BCC appear in higher rates than expected by chance, despite the fact that most other malignancies are found with reduced prevalence in this group of patients [43]. Additionally, epidemiological data on the frequency of *Malassezia* colonization in different animal species infer a role of this yeast in BCC induction. *Malassezia* yeasts and BCCs are commonly found in dogs and cats [44–46], but are both rare to absent in lagomorphs and rodents [47,48]. Furthermore, dogs and cats develop BCCs that accrue in the head and neck region [46], areas overlapping with animal's *Malassezia* niche [46]. Among dogs BCCs are more common in hairy animal breeds with long-pendulous ears (Saint Bernards, Scottish Terriers) [45], an anatomical trait that favor *Malassezia* overgrowth [44].

The core mechanism by which *Malassezia* yeasts could mediate their carcinogenic action is probably through the production of locally acting potent indolic AhR ligands [6,7]. There is no evidence that AhR regularly mediates tumor initiation in the framework of multistep carcinogenesis models, yet continuous activation of AhR by ligands like dioxin definitely supports tumor promotion

[48,49]. The relationship of rapidly metabolized AhR ligands, including most naturally occurring ones like ICZ and indirubin, to carcinogenesis is more complex as in nature AhR ligands usually occur as mixtures affecting complex molecular interactions with potentially variable biological outcomes. For example, in humans, the mixture of polycyclic aromatic hydrocarbons that constitute tar treatment in dermatology and possess substantial AhR ligand capacity did not increase the incidence of skin cancers in psoriasis and atopic dermatitis patients [50], despite the fact that it contains an array of recognized skin carcinogens in biologically meaningful concentrations, like benzo-*a*-pyrene [49]. According to these facts, the presence of AhR ligands of *Malassezia* origin in the skin could modify epidermal carcinogenesis through different mechanisms:

- (a) By affecting the immune state of the skin. BCCs grow within an immune tissue environment skewed towards a Th-2 cytokine dominant milieu [24,25]. A similar immune state deviation is a typical finding in skin lesions of seborrheic dermatitis associated with *Malassezia* yeasts growth [51]. Liberation of potent AhR ligands by *Malassezia* growing on the skin offers a plausible mechanism to link the presence of the yeast to the corresponding alterations of the immune state of the skin [32,36]. By producing AhR ligands *Malassezia* yeasts could have the ability to induce tolerance either through direct activation of the AhR in dendritic cells [52] or through local production of IL-10 [51] by keratinocytes.
- (b) By perturbing the homeostasis between cell cycle progression and apoptosis [53–55]. While slowly metabolized xenobiotic AhR agonists like dioxin may inhibit cell proliferation, AhR stimulation by carbinol-derivatives seems to promote cell cycle progression and cell proliferation through interaction with the retinoblastoma protein Rb1 [54]. Additionally, AhR was also shown to interact with the E2F1 and inhibit the E2F1-mediated apoptosis [55].
- (c) Certain AhR ligands increase the expression of matrix metalloproteinase-1 (MMP-1) in keratinocytes [56,57]. MMP-1 activation is a key event in decisive steps of tumor progression, like invasion [57].
- (d) By affecting the salvage/survival of initiated tumor cells [58] and by inhibiting cell senescence [36]. Both alterations may result to imbalance between cell proliferation and cell loss in favor of the former [59].
- (e) By intervening with the vitamin D metabolism in epidermal keratinocytes. Vitamin D protects epidermis from the development of non-melanoma skin cancer from UVR or chemical carcinogens through its modifying effects on the hedgehog and notch-beta-catenin pathways. Profound CYP stimulation resulting from AhR activation was shown to promote vitamin D degradation in a macrophage cell line [60]. Whether intracellular vitamin D degradation as a result of AhR induction can promote non-melanoma skin cancer development in the human epidermis is a potential mechanism that deserves further analysis.
- (f) By modulating UVR carcinogenesis of the epidermis. Recent studies have confirmed that UVR-associated cell damage is partly mediated through activation of the AhR by intracellular production of 6-formylindolo [3,2-*b*] carbazole (FICZ) [29,30]. It is reasonable to deduce that the availability of potent AhR ligands of *Malassezia* origin in the epidermis could interfere with this pathway with potentially synergistic carcinogenic end-results. Within this framework it cannot be excluded that besides affecting tumor promotion indolic *Malassezia* products could appreciably modify even UVR tumor initiation in the epidermis (Fig. 1).

- (g) Finally by modifying the activity of the hedgehog signaling pathway, the main target of molecular deviations in BCC induction [23]. Indirubin, that can be produced by *Malassezia* has been shown to effectively down-regulate glycogen synthase kinase 3 (GSK3) [61,62], that could result in modification of the Gli-binding protein SUFU through phosphorylation [62]. The net effect of hedgehog signaling modulations, i.e. potentiation or attenuation, depends on the background activity of this pathway [62]. This pathway's intersection underscores the potential of AhR activation to modify BCC carcinogenesis through interference with the hedgehog pathway.

The above evidence infer that *Malassezia* indoles would probably not initiate skin neoplasms *per se* but could modify promotion and progression of e.g. UVR initiated skin tumors. Within the above framework a key component of the proposed association to be dissected in future studies will be the behavior of *Malassezia* yeasts under UV irradiation. There is some evidence that *Malassezia* may sense ambient solar radiation and accordingly adapt its metabolism through differential synthesis of melanin and photoprotective indolic compounds *in vivo* and *in vitro* [6,63]. Clinical observations in connection with pityriasis versicolor, the typical dermatosis caused by this yeast, underscore the potential of *Malassezia* to modify the physiology of adjacent skin areas: hypopigmented pityriasis versicolor skin lesions are resistant to sunburn contrary to the neighboring healthy skin [64] and pityriacitrin, an indole derivative produced by *M. furfur* possesses distinctive UV protective properties [5]. Thus, adaptation of *Malassezia* metabolism to the level of incident solar radiation seems to be a biochemical mechanism that has the potential to influence the microenvironment of the neighboring skin.

Future research

Herein we propose that *Malassezia* skin flora constitutes an appreciable local modifying factor of skin carcinogenesis, particularly through the production of potent AhR agonists (malassezin, ICZ, indirubin) [6–9]. Studies on the impact of chemical AhR modulation on photocarcinogenesis are needed to clarify the implication of *Malassezia* in skin carcinogenesis. Future research should dissect the role of the aforementioned indolic compounds on the hedgehog pathway, particularly in association with AhR mediated UVR effects (Fig. 1) as well as their effects on the skin immune vigilance. In this context the effects of either purified substances (i.e. ICZ or indirubin) or AhR ligands in mixtures extracted from controlled *Malassezia* cultures could be explored [8]. In particular, given the central role of the regulation of cell proliferation for carcinogenesis [65] research should initially focus on dissecting the biochemical mechanisms by which indolic compounds can modulate the cell cycle of epidermal cells. At the tissue level studies on the induction of immunological tolerance through AhR activation in the skin [66] could further clarify the role of *Malassezia* in promotion processes leading to skin neoplasia.

Recent phylogeographical and molecular epidemiology findings indicate that *Malassezia* yeasts survive on the skin as commensals, or sometimes pathogens, through a strict selection process [67,68]. These yeasts interact with the skin and shift through the symbiosis/parasitism to the infection status during our lifetime. The consequences of this dynamic adaptation process on the homeostasis of the host's skin, is far from being adequately understood. Human carcinogenesis in association with chronic latent infections is a well-established consequence of infestation and parasitism by a number of viruses (human papilloma virus, Merkel virus) [69,70],

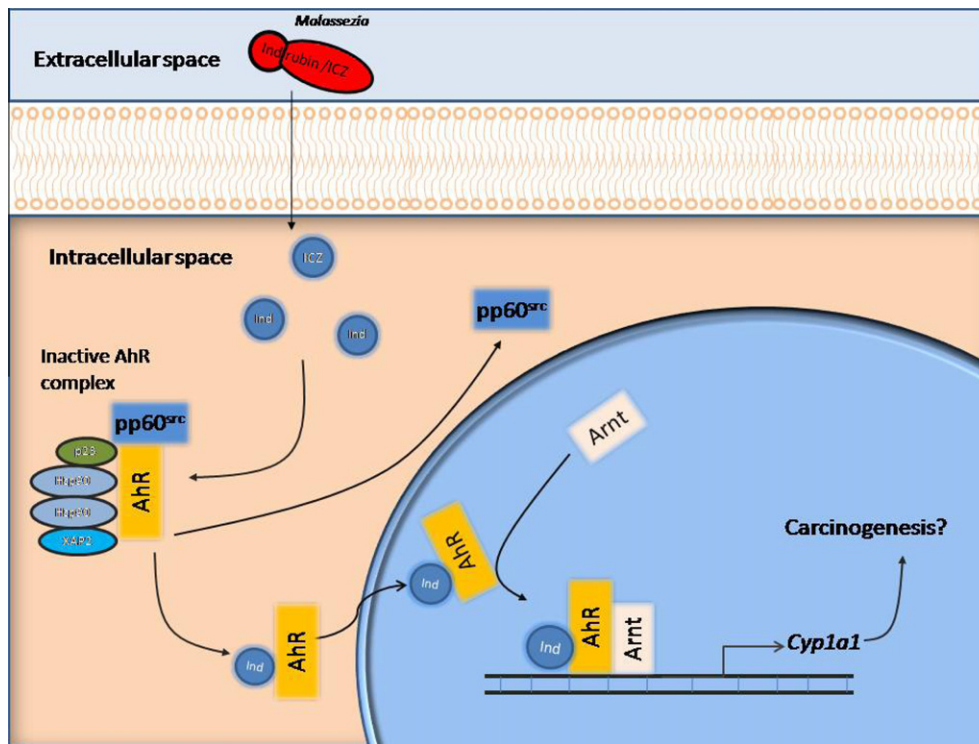


Fig. 1. Aryl-hydrocarbon receptor (AhR) activation in association with ultraviolet radiation induced skin carcinogenesis. Intracellularly formed 6-formylindolo[3,2-b]carbazole that mediates part of the UV response results in AhR activation and participates in skin carcinogenesis [29,30]. The ubiquitous skin commensal/pathogen *Malassezia* yeasts have the capacity to synthesize potent AhR ligands [indirubin (ind), indolo[3,2-b]carbazole (ICZ), malassezin] which can interfere with AhR activation and downstream pathway effects, resulting in skin carcinogenesis modification.

bacteria (*Helicobacter pylori*) [71] and trematodes (*Schistosoma*) [72]. Thus, in addition to “pathogenic” and “non-pathogenic” *Malassezia* species subtypes, future studies on AhR activating *Malassezia* metabolites and their effect on the skin immune system, might also lead to the recognition of ‘high’ and ‘low risk carcinogenic’ *Malassezia* subtypes.

Conflict of interest

The authors have no conflict of interest.

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