Review

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Dissecting the enigma of scleroderma: possible involvement of the kynurenine pathway

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Abstract: The kynurenine pathway (KP) is the metabolic pathway via which L-tryptophan is converted to nicotinamide. It serves important immune-regulatory roles. This article will review the evidence for involvement of the KP in scleroderma and present a possible model of kynurenine regulation of the cytokine cascade.

Keywords: aryl hydrocarbon receptor; kynurenine; scleroderma; TH2; transforming growth factor β.

Introduction

Cutaneous sclerosing disorders, frustratingly, are incompletely understood and treatments fall short of ideal. These disorders are associated with considerable morbidity and mortality with systemic sclerosis having the highest case specific mortality of any of the autoimmune rheumatic disorders [1].

Whilst an increased understanding of cytokine function has improved our understanding of this class of disorders, the mechanisms via which the cytokine cascade is controlled remains elusive.

This article will review the current evidence for the involvement of the kynurenine pathway (KP) in this group of disorders and present a possible model of kynurenine control.

Clinical considerations

Dermatologists define cutaneous sclerosis as scleroderma. They further divide it into diffuse variants and variants which involve the skin only. The diffuse variants may display pulmonary, renal, cardiac and oesophageal involvement or oesophageal involvement only. The latter is known as limited diffuse systemic sclerosis. Previously the acronym CREST syndrome *(Calcinosis, Oesophageal Dysmotility, Sclerodactyly, Telangiectasia)* was used to describe this syndrome. In limited disease, the skin below the elbow and knees is involved with some cases displaying involvement of the face. In diffuse disease skin proximal to the elbows and knees is involved.

Scleroderma may involve the skin only. This is known as morphea. There are different classification systems but clinically several variants are recognised including fronto-parietal, plaque, linear, subcutaneous, keloidal, diffuse and a pan sclerotic variant with extension as far as bone. Atrophic variants known as atrophoderma of Pasini and Parini, Parry-Romberg syndrome and linear atrophoderma of Moulin are recognised. Many consider eosinophilic fasciitis part of the morphea spectrum [2].

Aetiology

The aetiology of these disorders is unknown but traditionally, they are viewed as falling within the spectrum of autoimmune disorders due to their known association with other autoimmune disorders [3] and the presence of autoantibodies [2]. Triggering factors include trauma, infection, medications and radiotherapy [4].

Transforming growth factor β (TGF-β) is a major fibrotic cytokine and its expression is altered in scleroderma [5]. It is secreted as a large latent complex (LLP) that includes the active cytokine, a dimer of its processed N-terminal pro-peptide (latency associated peptide or LAP) and one of the three latent TGF-β binding proteins (LTBP-1, -3, or -4) [6].

Infantile stiff skin syndrome, a rare form of congenital scleroderma with a poor prognosis [7] provides an interesting insight into the possible pathogenesis. This disorder is due to mutations in fibrillin 1. Elastin and oxytalan fibres are components of the extracellular matrix and impart elastic properties to the skin. Elastic fibres consist of an amorphous component, predominantly composed

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of cross-linked elastin built upon a scaffold of microfibrils. Fibrillins of which there are three types (fibrillin 1, 2 and 3) are glycoproteins polymerised end to end to form the microfibrils. Fibrillin-1 is a binding site for cellular integrin's enabling cells to bind to and interact with the extracellular matrix. Fibrillin regulates the activity of TGF-β by acting as a target for the LTBP's sequestrating TGF-β in the extracellular matrix.

Antibodies to fibrillin 1 have been detected in both morphea [8] and scleroderma [9] as have antibodies to matrix-metalloprotein-1 (MMP-1) which inhibit collagenase activity [10].

It has been proposed that the initial injury is endothelial [11]. Interstitial oedema, fibrosis, basal lamina lamellation and endothelial swelling have been demonstrated in systemic sclerosis patients compared to controls irrespective of clinical features or disease duration [12]. This may be mediated by viruses [13] as cytomegalovirus (CMV) RNA transcripts have been found in the endothelium of patients with sclerodermoid changes [14]. In due course, this leads to altered production of collagen and other connective tissue molecules. The shift to TH2 dominance leads to the production of anti-endothelial antibodies [15] which further promote endothelial damage.

Unlike the other connective tissue disorders, the cytokine profile is skewed towards TH2 dominance [16] leading to peripheral blood eosinophilia, although the cellular infiltrate in these disorders is initially monocytic [17].

The kynurenine pathway

The KP is the metabolic pathway by which the essential amino acid L-tryptophan is converted to nicotinamide. Yet its role extends beyond contributing to the body's nicotinamide requirements. L-tryptophan is the least common of the essential amino acids and its availability is a rate limiting step for protein synthesis and thus cell division [18, 19]. T cells monitor L-tryptophan availability in their microenvironment via a GCN2 kinase [20], activation of which can lead to anti-proliferative and apoptotic effects [21]. This combined with the capacity to rapidly deplete the micro-environment of tryptophan via shunting to nicotinamide allows this metabolic pathway to exert powerful immunomodulatory effects. The rate limiting enzyme is indoleamine 2,3-dioxygenase (IDO) [22]. It is potently induced by interferon γ [23] thus providing a negative feedback loop during immune stimulation. In addition to IDO, other enzymes are involved in tryptophan breakdown.

Yet the relationship between the KP and the T cell response is even more complex. Metabolic intermediates in the pathway have been shown to have important regulatory roles promoting apoptosis of TH1 but not TH2 cells [24] thus favouring a TH2 shift in the cytokine response.

Not unexpectedly, this has evolved to fulfil critical physiological roles. IDO expression varies between tissues being maximal in interface tissues such as the gastrointestinal tract, respiratory system, placenta and skin [25] where exposure to foreign antigens is common and immunological tolerance is desirable. In fact, Munn's work demonstrating inhibition of this pathway by methyl-tryptophan led to a loss of immunological tolerance during pregnancy, established the significant immune-regulatory role played by this pathway [26].

During the 1980s, L-tryptophan supplements were widely used as a natural alternative to antidepressant medication based on the assumption that taking the precursor amino acid would increase synaptic levels of serotonin. Soon reports of eosinophilia myalgia syndrome [27] and eosinophilic fasciitis [28, 29], associated with the ingestion of L-tryptophan were received. Although initially linked to a contaminant in a product made by a single manufacturer [30], authors soon reported the same reaction to L-tryptophan produced by other manufacturers [31]. Activation of the KP was reported in these patients [32], as it was in patients with the so-called toxic oil syndrome [33]. This was reported in Spain in 1981, as a result of adulterated rapeseed oil and shared many features in common with eosinophilia-myalgia syndrome and eosinophilic fasciitis, the latter considered by many to be part of the morphea spectrum [2]. Quinolinic acid is a downstream metabolite of the KP. In an experiment, quinolinic acid administered to a human volunteer resulted in peripheral eosinophilia and a mixed neutrophilic and eosinophilic subcutaneous infiltrate with immunohistochemical studies demonstrating TGF factor β staining in dermal dendritic cells and vascular endothelium supporting the relationship between kynurenine metabolites and this class of disorders [34].

Not all cells have the enzymatic repertoire to produce nicotinamide adenine dinucleotide (NAD), despite their ability to convert tryptophan to kynurenine [35, 36]. The initial segment of the pathway which involves the conversion of L-tryptophan to kynurenine is ubiquitous. The second segment of the pathway in which 3-hydroxykynurenine is metabolised to quinolinic acid is limited

to hepatocytes and leucocytes, while the final conversion of quinolinic acid to NAD takes place in hepatocytes only.

The aryl hydrocarbon receptor (Figure 1)

The aryl hydrocarbon receptor (AHR) is a cytosolic receptor for low molecular weight molecules maximally expressed in interface tissues [37, 38]. Its major function is the metabolism of exogenous toxins via the cytochrome P450 pathway in association with the Nrf2 anti-oxidant pathway which also contains xenobiotic response elements (XRE) [39]. In the cytosol, the AHR exists in a latent state as part of a multiprotein complex (Figure 1) which includes the heat shock protein 90 (hsp90), heat shock protein 23 (hsp23) and hepatitis B virus X-associated protein 2 (XAP2) [40]. A signalling partner proto-oncogene c-Src ($Pp60^{src}$) is released into the cytosol on ligand binding attaching to the epidermal growth factor receptor (EGFR) activating mitogen-activated protein kinase (MAPK) signalling [41, 42].

On ligand binding, the receptor complex translocates to the nucleus [43] binding to the aryl hydrocarbon receptor nuclear transporter (ARNT). The AHR-ARNT heterodimer subsequently interacts with genes containing XRE.

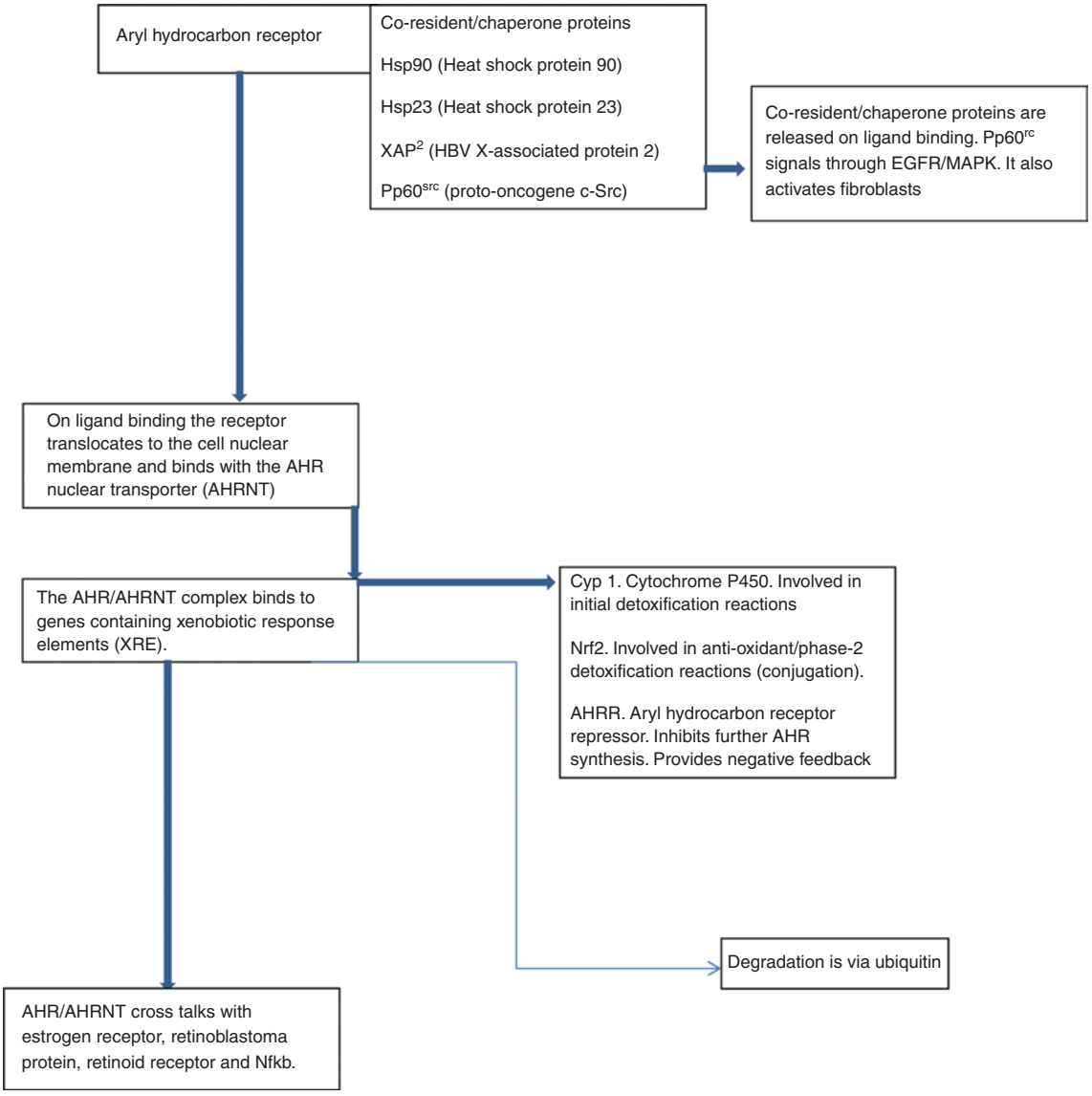

Figure 1: Schematic diagram of the aryl hydrocarbon receptor and its co-resident/chaperoning proteins outlining the mechanisms of action.

There is also crosstalk between the AHR and the estrogen receptor [44], the retinoblastoma protein, thus inhibiting cell cycle progression [45] and the retinoic signalling pathways [46]. The AHR can also bind the p65 subunit of nuclear factor κ light chain enhancer of activated β cells (NF-κB), thereby either suppressing or activating (depending on cellular context) the expression of NF-κB-dependent genes [47, 48].

Negative feedback is provided by ubiquitin mediated degradation [49] and AHR mediated expression of a repressor protein, the aryl hydrocarbon receptor repressor (AHRR) [50].

The relationship between the cytokine profile and the aryl hydrocarbon receptor

In the early stages of scleroderma, Th1 cells and TH17 cells are proposed to dominate the immune profile [51] later shifting to TH2 [16]. The AHR facilitates the development of the TH17 subset and their cytokines IL-17 and 22 [52] both of which have been identified in children with morphea [51]. TH17 lymphocytes promote the expression of the pro-fibrotic cytokines in scleroderma [53]. In addition, $pp60^{src}$ released from the AHR on ligand binding plays a role in fibroblast activation [54].

The relationship between the kynurenine pathway and aryl hydrocarbon receptor

Several KP metabolites are physiological ligands for the AHR [55–57] thereby integrating the KP with both the initial Th17 dominance followed by the subsequent shift to a TH2 as the KP metabolites promote apoptosis in TH1 lymphocytes.

A proposed model (Figure 2)

Endothelial injury leads to expression of vascular endothelial growth factor (VEGF) [58], a known inducer of the rate limiting step in the KP IDO [59]. Downstream kynurenine metabolites promote a TH2 shift in the immune system [24, 60] favouring IL-4 secretion, B cell switching and antibody production. This environment enables the generation of anti-fibrillin antibodies which may interfere with the targeting of the LTBP's to the extracellular matrix leading to increased production of the extracellular matrix.

TGF-β is known to sustain IDO expression [61], allowing the continued generation of kynurenine metabolites, thus enhancing the fibrotic response. Finally, many kynurenine metabolites are natural ligands of the AHR [55–57] promoting further TGF-β production.

Fibrocytes are CD34+ cells which are recruited from the circulation to sites of injury. During tissue remodelling, they lose CD34 expression and gain smooth muscle actin (SMA) becoming myofibroblasts. Interestingly and counterintuitively, activation of the AHR with endogenous AhR ligand 2-(1′*H*-indole-3′-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) inhibits myofibroblast differentiation [62]. Yet the AHR has been described as a Janus-faced receptor behaving in a non-canonical fashion in inflamed tissues [63] and thus it is plausible that KP metabolites acting through the AHR may promote the myofibroblast differentiation seen in morphea [64].

In an immunohistochemical study, involving a small number of patients with morphea at our institution, activation of the KP was noted in the epidermal basal layer, eccrine units and vascular endothelium in involved compared to non-involved tissue [65]. In a more recent study involving peripheral blood mononuclear cells, it was determined that monocytes but not lymphocytes express the KP [66]. In morphea, the initial cellular infiltrate is monocytic [17]. The resultant catabolism of tryptophan would be expected to skew the subsequent lymphocytic infiltrate towards TH2. In our study, it was not possible to determine the nature of the infiltrating mononuclear cells except that all did not express the KP, so the results would be consistent.

Further supporting evidence

Loss of adnexal structures

Loss of adnexal structures and subcutaneous fat is seen in advanced morphea. Epithelial mesenchymal transition (EMT) is the process by which epithelial cells lose their adhesion proteins and gain migratory properties thus transforming into mesenchymal stem cells. TGF-β is one of several cytokines involved in EMT [67] and EMT has been reported as a possible cause of fibrosis of

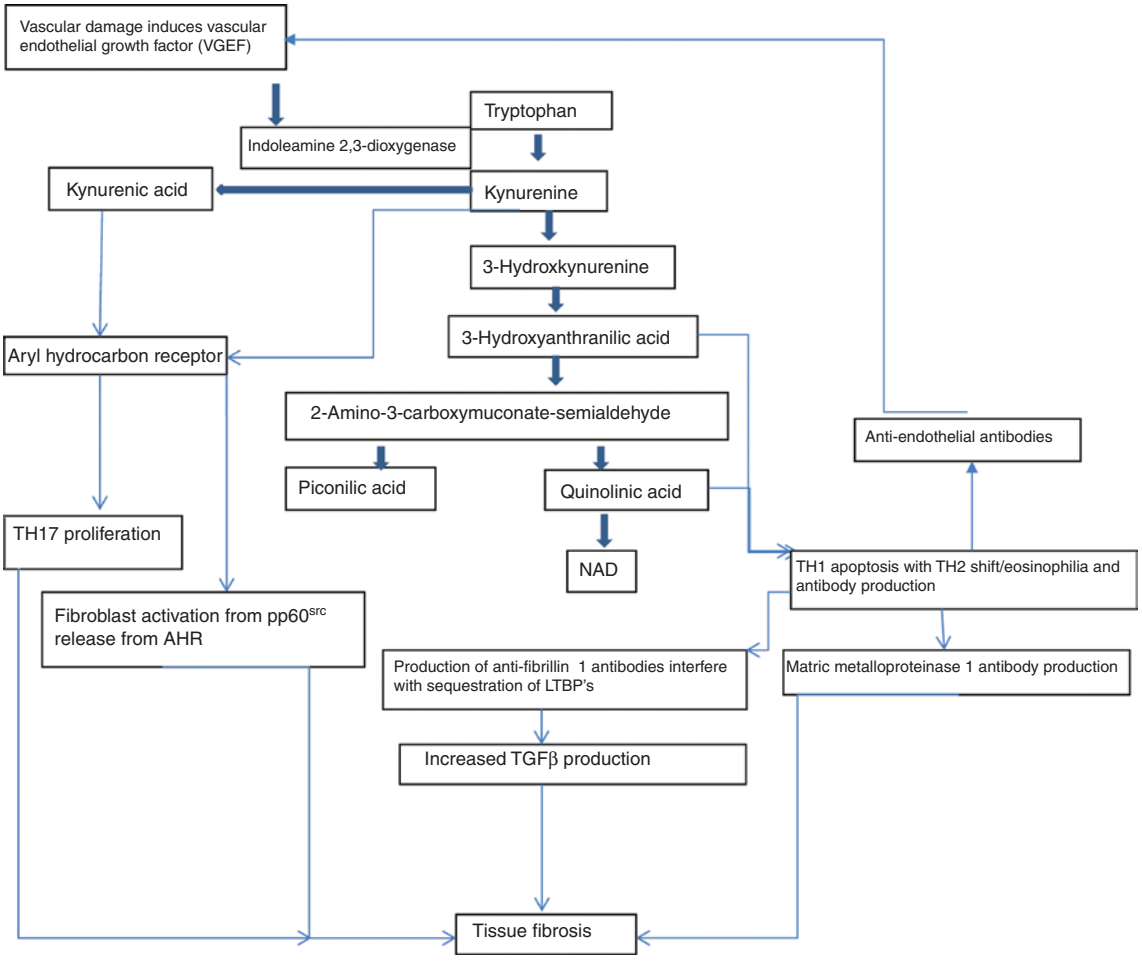

Figure 2: Proposed model outlining the involvement of the kynurenine pathway in scleroderma.

the eccrine units in morphea [68]. Interestingly, in our small study, strong expression of the KP was found in the eccrine unit [65].

Raynaud's phenomenon

The diffuse variants of scleroderma are characterised by Raynaud's phenomenon (chronic episodic digital ischemia) which is absent in the cutaneous variants. The cause is unknown but nitric oxide is thought to play a role and one of the KP metabolites 3-hydroxyanthrinilic acid is known to inhibit the expression and activity of inducible nitric oxide synthetase [69]. Although speculative, the final phase of the KP is expressed only in hepatocytes. Scleroderma most commonly affects interface organs with intrinsic high IDO activity. Venous return from these organs most commonly drains to the superior vena cava prior to distribution through the pulmonary vasculature, left heart and arterial circulation. This allows distribution of 3-hydroxyanthrinilic acid to the upper half of the body before return to the liver which could conceivably account for the Raynaud's phenomena seen in systemic disease.

Neurological symptoms

Most research on kynurenines has focused on their role in neuro-inflammation [70–72] and neurological symptoms have increasingly been reported in scleroderma [73].

Relationship to environmental factors

Scleroderma has established associations with exposure to organic solvents [74] many of which are ligands for the AHR through which many of the activities of the KP are expressed.

Morphea may follow radiotherapy for breast carcinoma with an incidence if 1:500 [75]. Radiotherapy is a recognised cause of endothelial injury [76] thus supporting the concept that the initial injury is endothelial.

Tranilast

Tranilast is a structural and functional analogue of the kynurenine metabolite anthranilic acid which is available in Japan and South Korea and is used in the management of both allergic and scarring disorders. It inhibits both fibroblast proliferation [77] and TGF-β action [78]. There have been anecdotal reports of success in morphea [79] and the agent has been shown to manipulate the KP in a human subject [36]. We are currently conducting a trial at our institution comparing the efficacy of topical corticosteroids compared to a topical corticosteroid and tranilast combination in morphea [80].

Conclusion

There is strong evidence of the involvement of the KP in sclerosing cutaneous diseases principally via orchestration of the cytokine cascade and the establishment of a TH2 dominated immunological environment. Many effects of the KP are mediated via the AHR, several metabolites of which are physiological ligands.

It is proposed that endothelial damage leads to activation of the KP via VEGF. KP metabolites activate the AHR, facilitating the development of the TH17 subset of lymphocytes which subsequently secrete pro-fibrotic cytokines. $Pp60^{src}$ liberated from the AHR complex activates fibroblasts. Downstream KP metabolites promote the apoptosis of TH1 with the preservation of TH2 cells leading to the development of auto-antibodies. Anti-fibrillin 1 antibodies interfere with binding of the LTBP's promoting further tissue fibrosis. Antibodies directed against MMP-1 inhibit collagenase activity and connective tissue cycling. Anti-endothelial antibodies promote further vascular damage perpetuating the cycle.

Current recommended management is via non-targeted immunosuppression with the best evidence for corticosteroids, methotrexate and mycophenylate mofetil [81]. Targeting the KP may provide additional and more targeted therapy for this group of disorders.

Conflict of interest statement: The author has declared no conflicts of interest.

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