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## Viewpoint

**Vitiligo and psychological stress: A hypothesis integrating the neuroendocrine and immune systems in melanocyte destruction****Mohammed S. Al Abadie,<sup>1</sup> Chayada Chaiyabutr,<sup>2</sup> Kinari X. Patel,<sup>3</sup> and David J. Gawkrödger,<sup>4</sup>**

<sup>1</sup>Department of Dermatology, North Cumbria Integrated Service NHS Trust and the University of Central Lancashire Medical School, Preston, UK, <sup>2</sup>Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, <sup>3</sup>Imperial College Healthcare NHS Trust, St Mary's Hospital, London, UK, <sup>4</sup>Department of Dermatology, University of Sheffield Medical School, Sheffield, UK

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**Correspondence**

David J. Gawkrödger  
Department of Dermatology  
University of Sheffield Medical School  
Beech Hill Road  
Sheffield S10 2RX  
UK

E-mail: [d.j.gawkrödger@sheffield.ac.uk](mailto:d.j.gawkrödger@sheffield.ac.uk)

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Vitiligo is an acquired disease, characterized microscopically by the destruction of neural-crest-derived melanocytes, that may be precipitated by local skin trauma, mental stress, and chemical imbalances, all of which suggest neuroendocrine involvement.<sup>1</sup> Here, we examine hypotheses by which psychological stress might influence melanocyte destruction through immunoendocrine pathways involving cytokines and neuropeptides.

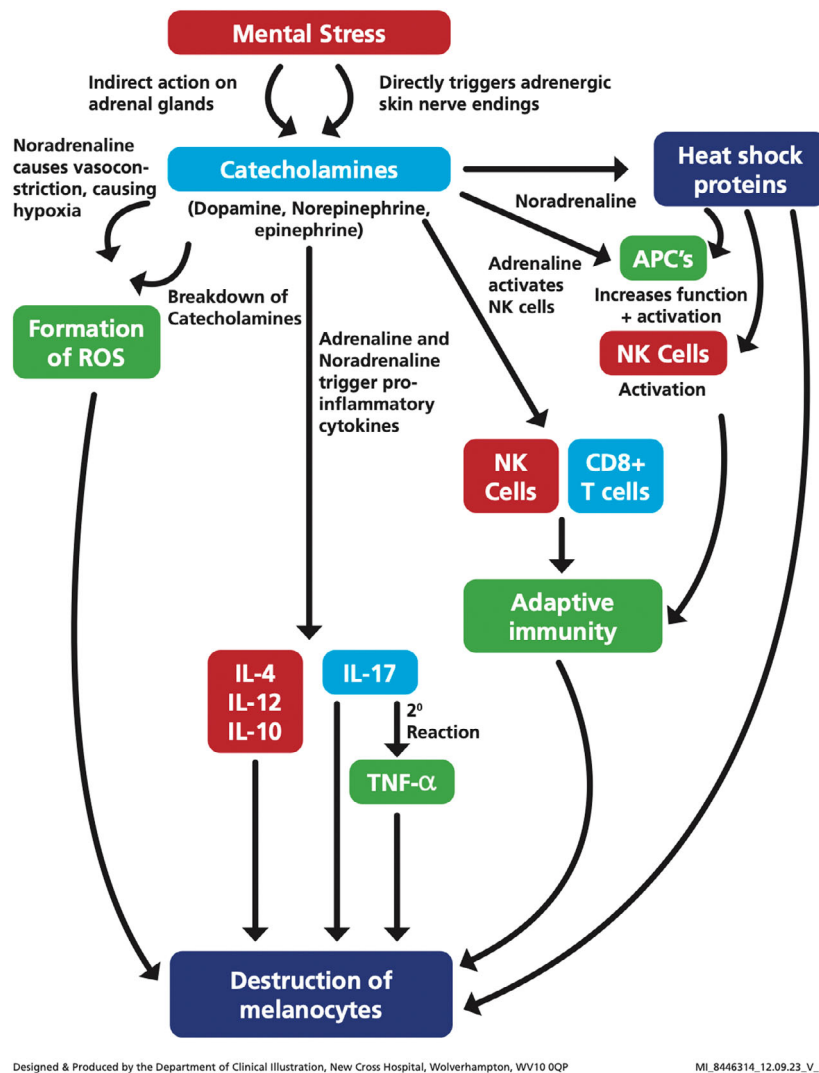
First, we summarize laboratory and clinical evidence. The inextricable link between psychological stress, neuroendocrine function, and immunity makes unsurprising a proposal for the interplay between these systems and melanocyte destruction in vitiligo. Animal studies support this proposition. Stressed mice

show raised catecholamines, reduced pigmentation, increased unpigmented hairs, and loss of melanocyte stem cells.<sup>2</sup> Metabolic stress, defined by the cortisol to dehydroepiandrosterone sulphate ratio, is reported in patients with vitiligo and is an antecedent of disease onset.<sup>3</sup> 56% of 535 patients noted stress triggered their vitiligo,<sup>4</sup> and 57% of 1541 described at least one major life event in the 2 years preceding onset (though no relation to disease extent nor type).<sup>5</sup> The apparent psychological effect of having vitiligo impairs research in this area.

Next, we propose the hypothesis that psychological stress, via neuroendocrine-related immune influences, might induce

oxidative stress that destabilizes melanocytes and makes them susceptible to attack by antigen-presenting cells and specific T cells. The central response to psychological stress—release of hypothalamic corticotrophin-releasing hormone and pituitary adrenocorticotrophic hormone with consequent adrenal release of corticosteroids and catecholamines—is accompanied by the peripheral discharge of catecholamine from skin nerve endings and skin cells, both pathways controlled by feedback.<sup>6</sup> Catecholamines generate toxic free oxygen radicals directly and via vasoconstrictive hypoxia (more so in those with genetically determined low levels of radical scavengers).<sup>6</sup> They additionally act on  $\alpha$  and  $\beta$  adrenoreceptors to release melanocyte destructive IL-4, IL-10, IL-12, and IL-17 (the latter of which can initiate TNF- $\alpha$ —a key factor in pigment cell damage) and activate innate and adaptive immunity, for example, via CD8<sup>+</sup>,

NK and antigen-presenting (APC) cells (Figure 1). Furthermore, catecholamines stimulate heat shock proteins (HSP)—which themselves augment APC activity and amplify immune responses through reactive oxygen species (ROS) and cytokines—and can directly reduce melanocyte adhesion.<sup>7</sup> It is proposed that the above neuroendocrine influences can enhance the innate immune milieu both through the molecular means of ROS (acting as damage-associated molecular patterns) and iHSP70 (from damaged cells), through raised levels of circulating and intracutaneous immune cells (NK, dendritic and macrophage) and via the regional lymph node located stimulation of adaptive anti-melanocyte cytotoxic T cells.<sup>8</sup> The CD8<sup>+</sup> and CD4<sup>+</sup> lymphocytes seen in vitiligo epidermis release type 1 cytokines (e.g., IFN- $\gamma$ , TNF- $\beta$ ) which recruit further melanocytotoxic cells.



**Figure 1** Mechanisms by which catecholamines may damage melanocytes (adapted from Yu et al.<sup>6</sup>)

We suggest an additional, parallel but related, direct, and indirect, mostly local melanocyte-destructive role for neuropeptides released from cutaneous nerve endings in response to psychological stress.<sup>6</sup> Neuropeptide Y (NPY), demonstrated to be present in active vitiligo areas and to induce dysfunction in melanocytes,<sup>1</sup> is released from the hypothalamus in response to mental stress. Systemically, NPY is a vasoconstrictor that can stimulate endothelial nicotinamide adenine dinucleotide phosphate and result in ROS with consequential melanocyte damage. Other neuropeptides can act locally. Cutaneous release of calcitonin gene-related peptide by psychological stress can activate APCs and mast cell release of TNF- $\alpha$ ; the local release of substance P is immune-chemotactic, and nerve growth factor and its receptor can stimulate the melanocyte to destruction.<sup>1,6</sup>

Here, we have demonstrated mechanisms by which psychological stress, via neuroendocrine and neuroimmune pathways, could influence the immune response, which is generally agreed to be mainly responsible for melanocyte destruction in vitiligo. To regard vitiligo as uniquely an immunological disease is to ignore several pillars of clinical evidence. The immune pathways operate within the chemical environment of the body. In this article, we suggest areas for further research to better illuminate how these systems might be pathologically interconnected in vitiligo.

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