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NEWS AND COMMENTARY

Neuritin, unmasked as a checkpoint for the pathogenesis of allergy and autoimmunity

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In March 2021 in *Cell*, Gonzalez-Figueroa *et al*.[1] identified that follicular regulatory T cells (Tfr) in the germinal centre suppress the development of B-cell-driven autoimmunity and IgE-mediated allergic sensitisation via their secretion of the neuropeptide neuritin. Although many questions remain about how neuritin secretion is regulated, especially what leads to a relative neuritin deficiency, which receptor it binds and how it can be modified, the authors present evidence that unmasks a lack of neuritin as a previously unrecognised critical contributor to the development of allergic and autoimmune disease. This novel insight, which highlights the dysregulation of the IgE and autoantibody-producing B cell at the centre of the pathogenesis of these diseases, is likely to aid clinical approaches currently based on the symptomatic treatment of disease to more focused and preventative strategies.

There is compelling evidence that regulatory T (Treg) cells are heterogeneous and can specialise through upregulation of lineage-specific transcription factors in response to environmental triggers. These subsets include FoxP3$^+$ Treg cells that are dedicated to suppress Th1, Th2 and Th17 cells, tissue-specific inflammation and antigen non-specific germinal centre responses[2], the latter identified as a Bcl6$^+$ Treg subset known as Tfr.[2]

Here, using a *Tfr*-deficient mouse model, Gonzalez-Figueroa *et al*. detail how, in the absence of Tfr cells, there is enhanced germinal centre plasma cell development, production of tissue-specific autoantibodies, IgE production, and susceptibility to IgE-mediated anaphylaxis upon antigen re-exposure. The authors then determine the mechanism by which Tfr cells mediate suppression of these immunopathologies. Previously, IL-10- and CTLA-4-mediated suppression has been implicated in this process[3,4]; however, whilst mice and patients who lack functional Treg cells develop the characteristics of B-cell-associated autoimmunity, mice that lack IL-10 or have defects in CTLA-4 do not have this phenotype. Having determined the importance of Tfr in the induction of aberrant B-cell responses, the authors reason that there might be other molecules involved and identified neuritin as being highly expressed in Tfr cells, based on a comparative transcriptional profiling analysis of Treg, Tfr, T follicular helper cells and naïve T cells.

The authors then characterise mice lacking neuritin in FoxP3$^+$ Treg cells, including Tfr cells. These mice demonstrated a two-fold increase in splenic BLIMP-1$^+$ CD138$^+$ plasma cells and had higher plasma levels of interferon-gamma and total IgG1. Similar to Tfr-deficient mice, these mice developed a range of tissue-specific autoantibodies. The administration of soluble neuritin was able to restore the functional defect of the Tfr-deficient mouse and repress rogue germinal centre plasma cell development, it also led to a downward trend of anti-histone autoantibodies. Furthermore, neuritin also mediated reduction in human B cells' IgE production. In line with these findings, neuritin-

deficient mice had higher total IgE and developed high titres of IgE antibodies against a model antigen (ovalbumin; OVA) after OVA immunisation. In the absence of neuritin-expressing Treg cells (or absence of Tfr cells), mice died within 10 min of anaphylaxis with a demonstrable serum histamine increase after a re-immunisation challenge with OVA.

Neuritin has been previously identified as a gene product, which is upregulated in stimulated neural tissue. It is expressed in two isoforms: a membrane-bound form, shown to be involved in the regulation of neuronal growth and the promotion of synapse formation,[5] and a soluble form, which in the developing brain regulates cortical progenitor cells by inhibiting caspase-mediated apoptosis. There is evidence that neuritin-mediated signalling results in activation of the ERK and mTOR signalling pathways, which is also utilised by growth factor signalling (Figure 1). Importantly, although candidate receptors that might bind soluble neuritin have been suggested, including the insulin receptor[6] and follicular growth factor receptor,[7] direct evidence of neuritin-specific signalling is yet to be demonstrated (Figure 1).

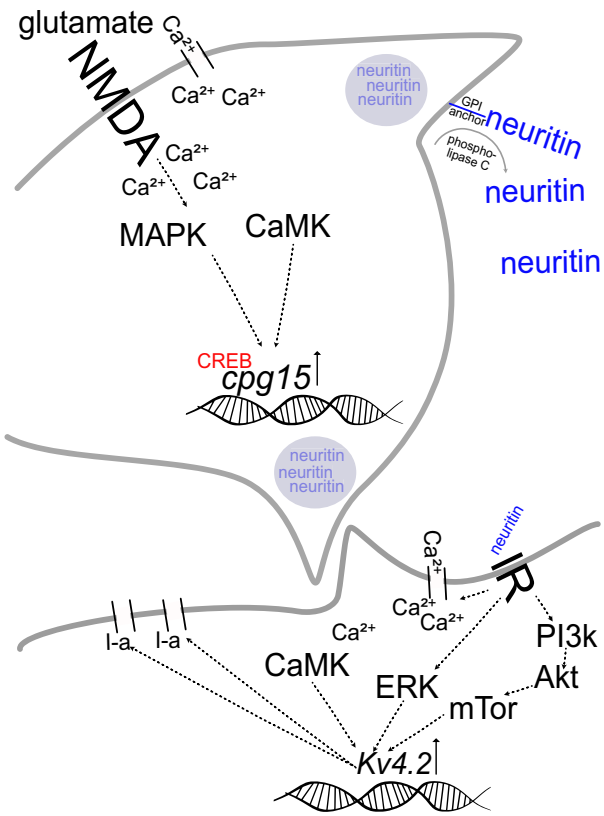

Figure 1. Overview of the known elements of neuritin signalling pathways. Activation of neurones via receptors such as the glutamate and ion channel protein receptor NMDA induces the cAMP response element-binding protein (CREB)-mediated transcription of the neuritin gene (cpg15). The neuritin protein accumulates in the cytoplasm and also becomes expressed on the plasma membrane anchored by a short GPI anchor region. Membrane-bound neuritin can be cleaved via phospholipase-C, induce signalling via presumed receptors that include the insulin receptor (IR), and initiate signalling via the extracellular signal-regulated kinase (ERK), PI3 kinase (PI3K) and the Ca^{2+} calmodulin-dependent protein kinase (CaMK) leading to the activation of genes including Kv4.2, resulting in a higher density of A-type potassium ion channels (I-a).

Screening for the expression of neuritin in human tissues indicates high expression in the placenta, lungs, skeletal muscle, thymus, pancreas, liver and heart tissues; lower levels in the small intestine, ovary, spleen and testes, but no detectable expression in the kidneys, colon, prostate or leucocytes. In cancer, neuritin 1 has been described as an angiogenic and hypoxia-induced factor.[8,9] An *in silico* analysis of RNA-sequencing data published on the GEPIA website (http://gepia.cancer-pku.cn/index.html) suggests that 13 of 31 human tumor types showed a significantly reduced neuritin mRNA message, whilst other studies, such as for gastric cancer[10] and melanoma,[11] showed a strong upregulation of neuritin 1 message. It is therefore possible that neuritin acts with biphasic biological effects (Figure 2).

The finding that a neuropeptide might be a regulator of autoimmune and allergic pathogenesis may seem counterintuitive and has generated in our minds a multitude of questions leading us to speculate on neuritin's role in the clinical manifestations of these diseases.

Australia is facing an allergy epidemic, with the latest data showing that 4–8% of Australian children experience food allergies.[12] Alarmingly, the rate of adults declaring food allergies has also risen to 2–3%.[12] Presentations of patients with severe allergic reaction to food, medications or insects, aka anaphylaxis, to our emergency departments have doubled in the last ten years. The worldwide prevalence of atopic dermatitis (AD) is also on the rise, ranging from 0.2% to 20%, with the highest rates seen in Andean Latin American children.[13] The onset of AD occurs predominantly in childhood, with nearly 20% of children with AD developing another allergic disease such as food allergy, asthma or allergic rhinitis.[14] There is a significant association

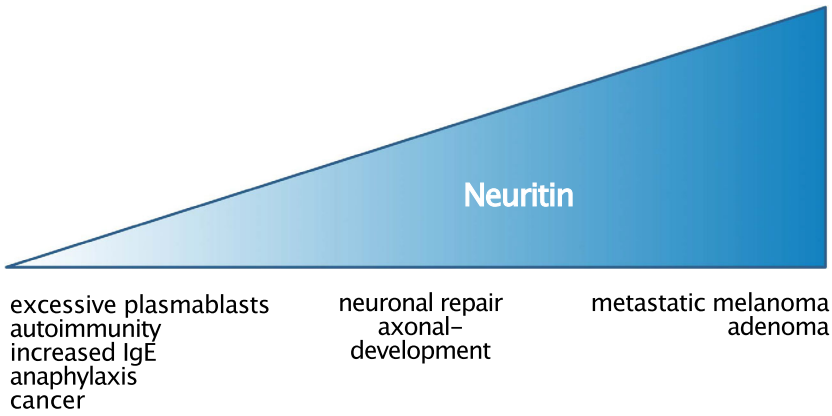

Figure 2. Varying neuritin expression is associated with different biological outcomes.

between the development of food allergies and AD, with cutaneous exposure to ubiquitous foods and allergens in infancy via a defective skin barrier being an important route of sensitisation to food allergens. Importantly, subjects with AD have very high serum IgE levels, which may be indicative of a disinhibition of IgE production. To date, nothing is known about the role of neuritin in the development of AD. However, there is clear evidence of the influence of the peripheral nervous system on AD,[15] with interactions likely between nerve fibres and mast cells.[16] It is plausible that neuritin may be part of the normal homeostatic regulation of the skin and its reduced expression either in the germinal centre, driving an atopic phenotype, or in the skin, might affect epithelial cell biology. Supporting this idea are case reports of increased skin rash when areas of skin have been denervated.[17]

Paralleling the increase in allergies in our societies is an increase in subjects with autoimmune diseases, with an overall estimated prevalence worldwide of 4.5%, with 2.7% presenting in males and 6.4% in females.[18] The close link between IgE, generally associated with allergy, and IgG1 autoantibody production initially seems surprising. However, it is important to recognise that several disease-causing autoantibodies are of the IgE isotype and this has been more recently termed by some 'autoallergy'.[19] This is often under appreciated as standard tests do not test for the IgE isotype but focus on the IgG isotype. Commonly, antibodies of both isotypes co-exist. Furthermore, IgG4 (a subclass that is not found in mice) antibodies, which can coincide with IgE autoantibodies, are often pathogenic (e.g. in pemphigus, an autoimmune blistering skin disease). It is therefore important that we remain open to the idea that the clinical manifestation of allergic disease and autoimmunity is a phenotypic spectra of dysfunctional B cells in the germinal centre. This is further supported by the fact that severe allergies can be treated with B-cell-targeted immunosuppression such as anti-CD20 agents.[20]

This recent paper by Gonzalez-Figueroa *et al*. will likely provoke the study of new therapeutic targets, namely treatment of allergies with B-cell-modulating agents and 'autoallergy' with therapeutics that target IgE-related allergic cytokines (such as IL-4, IL-5 and IL-13), or directly by specifically target IgE-producing B cells. How neuritin fits into these treatment algorithms remains to be seen and should be subject to further careful evaluation given its not only ubiquitous but also seemingly opposing beneficial effects, just like other factors that act at the interface between autoimmunity and protection from infection and cancer; it is a fine line to walk.

AUTHOR CONTRIBUTIONS

Michaela Lucas: Conceptualization; Writing-original draft; Writing-review & editing. **Andrew Douglas Lucas:** Writing-review & editing.

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