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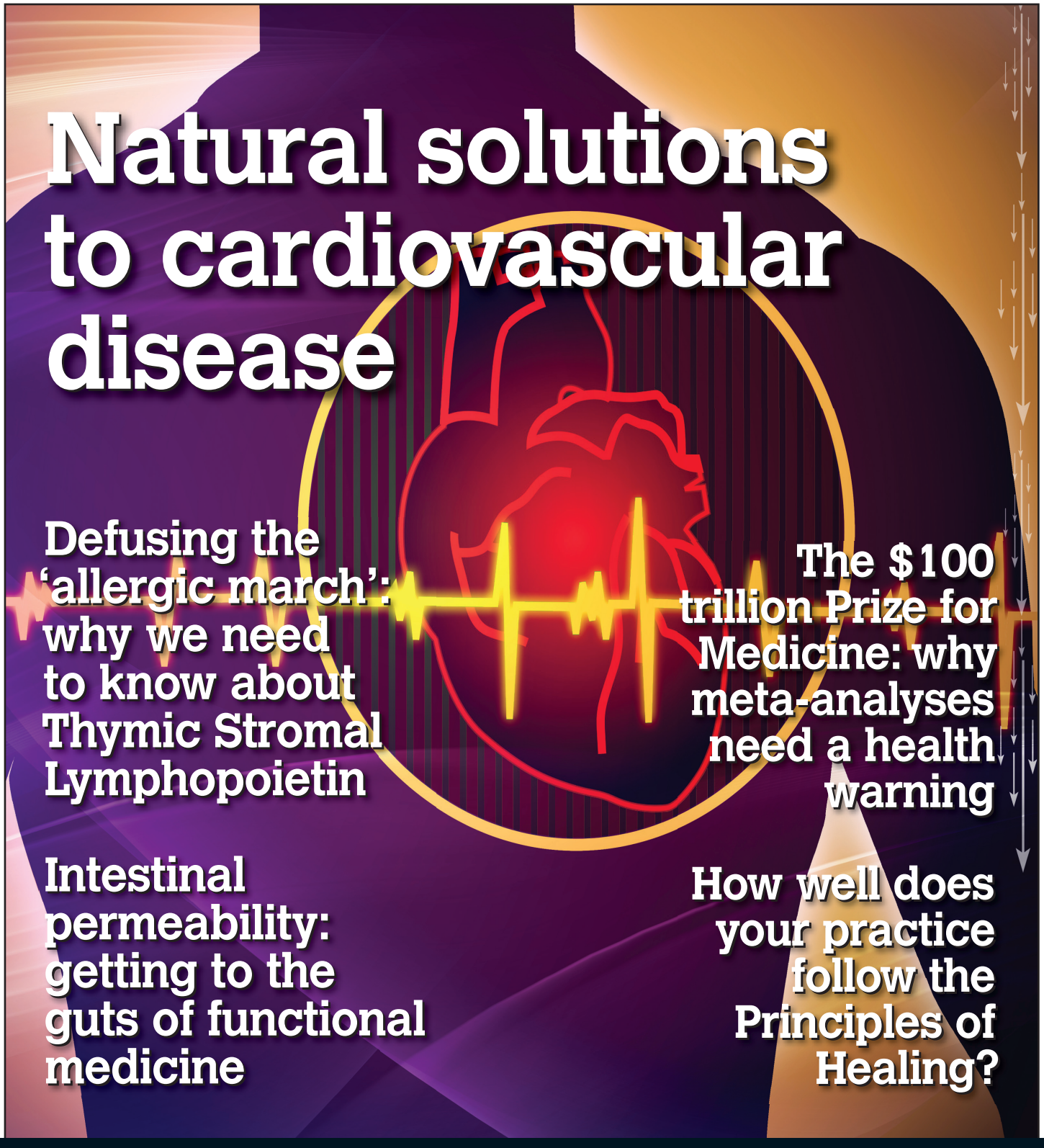

Defusing the 'allergic march': why we need to know about Thymic Stromal Lymphopoietin

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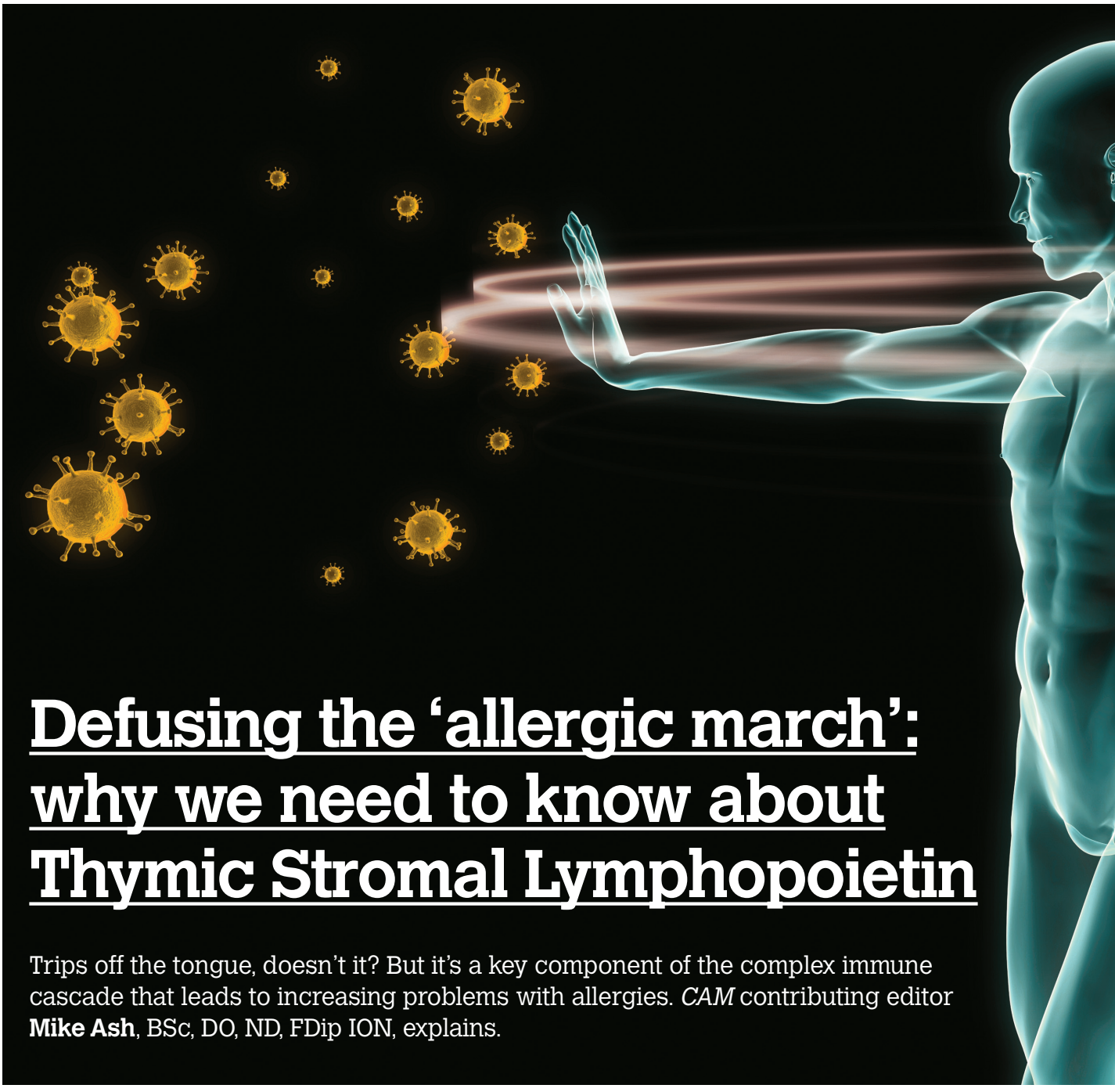


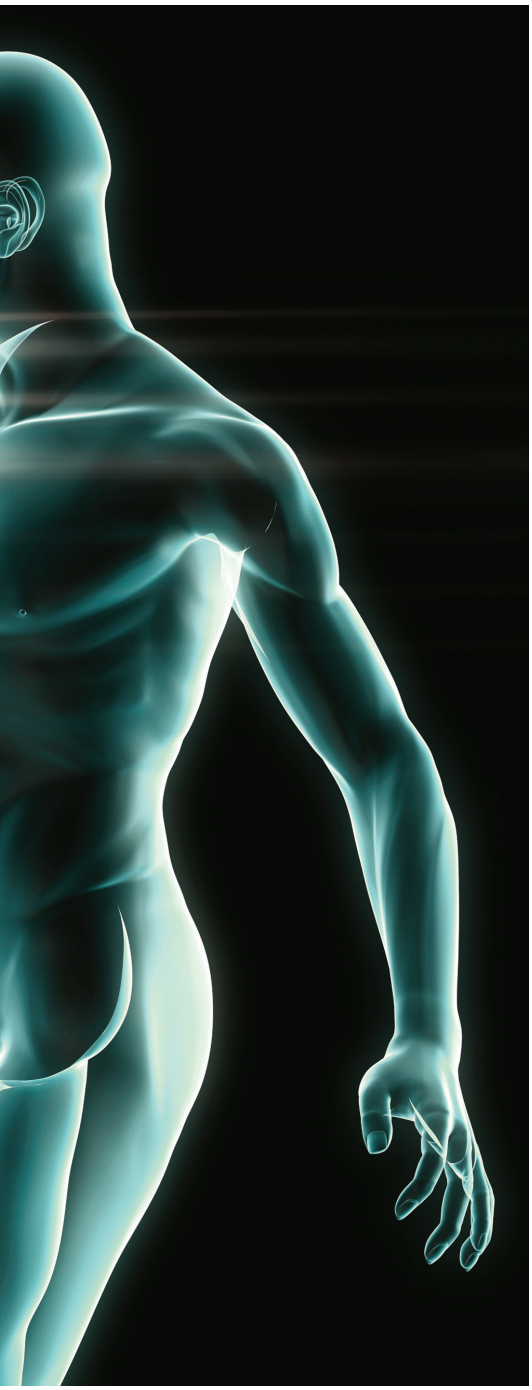
Defusing the 'allergic march': why we need to know about Thymic Stromal Lymphopoietin

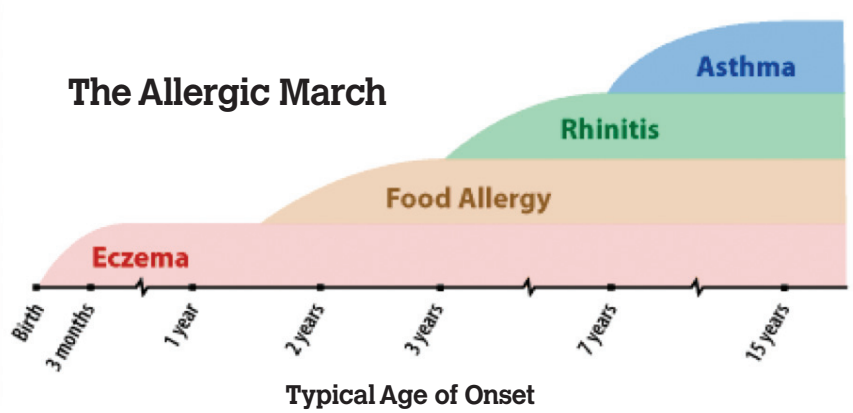
Trips off the tongue, doesn't it? But it's a key component of the complex immune cascade that leads to increasing problems with allergies. *CAM* contributing editor **Mike Ash**, BSc, DO, ND, FDip ION, explains.

Many CAM practitioners will consult with people who have a well-defined allergy or, in some cases, a range of symptoms that reflect an allergic response but that do not meet the recognised IgE assessment. Some of these people will also be experiencing what is known as the "allergic march" – the development of secondary allergenic profiles such as asthma after already having an established food allergy, such as peanut or shellfish.

The allergic march usually begins with eczema – a dry, red, scaly rash that causes considerable itching and discomfort. Eczema is most commonly diagnosed within the first few months of life. In a third to a half of children, eczema is associated with an underlying food allergy. Food allergies (peanut allergy, for instance) generally begin to appear within the first three years of a child's life. Food allergy can cause gastrointestinal problems (such as colic, diarrhoea etc) and in some cases, it can be life threatening. As children age further, the allergic march may proceed to the development of asthma and/or rhino-conjunctivitis (sometimes called hayfever).

The pattern of development of allergic diseases – what types of disease occurs





Typical Age of Onset

and the age at which they occur – is highly reproducible (ie the pattern is the same in a large proportion of children and increasingly in adults as well).

Allergy is the result of a complex immune cascade leading to the dysregulated production of Th2 cytokines, the generation of allergen-specific IgE-producing B cells and the subsequent activation and degranulation of mast cells upon allergen challenge.

TSLP (Thymic Stromal Lymphopoietin)

One of the principle cells known to play very important roles in the development and resolution of allergy and other complications related to adverse immune responses in the mucosal and epithelial tissues are dendritic cells (DCs). These cells, when brought into contact with TSLP, favour the allergenic profile – that is they convert naïve T cells into Th2 cells and amplify allergy risk and symptoms. (1) DCs are the professional antigen-presenting cells that have the capability to sense invaded pathogens and tissue stress, then present antigen to T cells, thereby bridging the innate and adaptive immunity.

What this mechanism has helped to us to understand is that local tissues, in this case the epithelial tissues themselves, have the capacity to influence immune responses that in turn drive adaptive immune outcomes.

This indicates that altered barrier quality and local inflammation may be a cause or at least an amplifier of allergenic inflammation via TSLP promotion. (2) Recent studies have revealed that various cell types other than epithelial cells and epidermal keratinocytes (such as mast cells, airway smooth muscle cells, fibroblasts, dendritic cells, trophoblasts, and cancer or cancer-associated cells) also express TSLP. (3)

Environmental factors such as Toll-like receptor ligands, a Nod2 ligand (innate immune signalling proteins), viruses, microbes (dysbiosis), allergen sources, helminths, diesel exhaust, cigarette smoke, and chemicals trigger TSLP production as well.

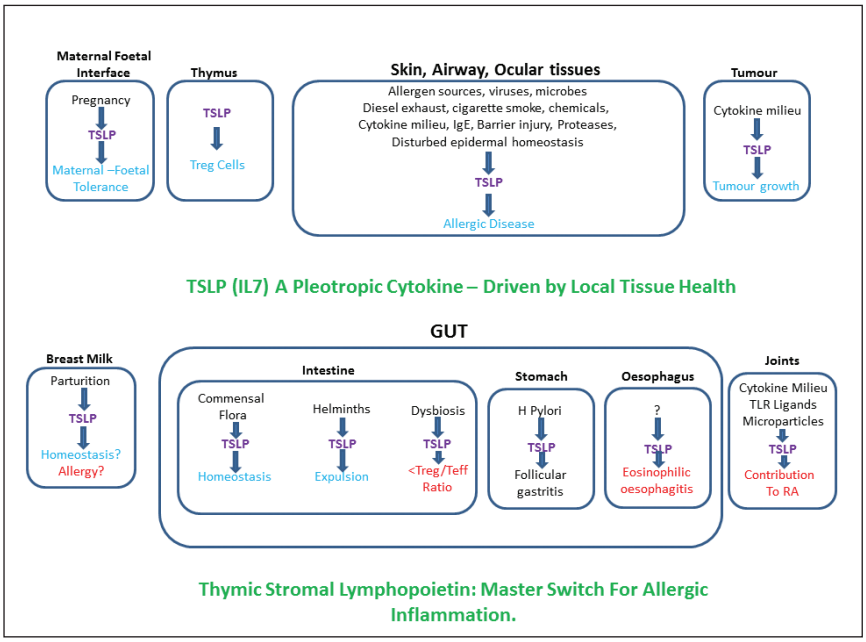
Compelling evidence implicates TSLP as playing a pivotal role in the pathobiology of allergic asthma and atopic dermatitis. (4) Other studies suggest it may have an amplifying effect in food allergy and inflammatory bowel disease. (5) These cross reactions suggest a critical role for TSLP as a driving factor in the emerging concept of tissue-specific control of immunity, with TSLP secretion at the epithelial-DC interface acting as an initial and amplifying factor in the pro-allergic cascade also known as the allergic march. (6)

What can we do

Apart from the interesting relationships between tissue health and immune reactivity, postulated some time ago by Polly Matzinger and colleagues, (7) the clinical question is: can we moderate inappropriate TSLP production and when and how should we do it? Is TSLP only problematic or can it confer benefit and does its role extend beyond the allergenic profile?

TSLP is capable of inducing tolerance during maternal foetal tolerance requirements, especially during early pregnancy. TSLP promotes Th2 and Treg cells required for a successful pregnancy. (8) TSLP may induce thymically originating regulatory T cells, by being expressed by the epithelial cells present in the thymic tissue. Centrally produced Treg cells have similar roles to those produced in the periphery – most commonly in the gut – but are still important players in maintaining human tolerance. (9)

Certain cancer cells, however, seem to proliferate more easily when exposed to TSLP. The cancer-promoting activity of TSLP primarily required signalling through the TSLP →



→ receptor on CD4(+) T cells, promoting Th2-skewed immune responses and production of immunosuppressive factors such as IL-10 and IL-13, so permitting cancer cells to avoid destruction. (10, 11)

Our stomachs may also be the worse off post-infection by H.pylori through the induction of TSLP, as the T cell phenotype altered towards the Th2 cell presentation favours chronic and follicular gastritis. (12)

Natural manipulation of TSLP

TSLP inhibition has been studied using three natural agents to determine their effectiveness in down-regulating its output. The mineral selenium (Se) has various effects – such as antioxidant, anti-tumour, anti-ulcer and anti-inflammatory. One paper suggests it can impact in a significant manner on the mast cell promotion of TSLP, indicating its potential use for inflammatory and allergenic illness. (13)

The same researchers have also identified the benefit can be repeated through the use of berberine and green tea extracts along with grapefruit juice. (14, 15, 16)

Other researchers have looked at the role of cis retinoic acid as a TSLP inhibitor via its action of the nuclear inflammation promoter NFkB and through the binding to the family of retinoic acid receptors (RAR) and the retinoid X receptors (RXR). (17)

The correction of any relevant dysbiosis, repair of barrier integrity and modification of diet selection to favour antioxidant-rich foods will also be part of the programme to modify TSLP, as it is driven in large part by the health of the local tissues.

The use of probiotics to increase IL-10 and TGF-Beta will also favour a T cell phenotype that regulates imbalances between Th2 and Th1 helper T cells.

Conclusion

TSLP is an interesting molecule that may represent a therapeutic target. We are unable to measure this cytokine for clinical purposes, but the strategy to apply for people with allergies, beyond the exclusionary principle of triggering foods or environmental exposure, permits us to approach the prevention or resolution with a key mechanism in mind.

Early days yet, but as more studies are done I expect a number of foods and food substrates will demonstrate benefit and may well reflect the genetic requirement for food selection.

About the author

Michael Ash, BSc (Hons), DO, ND, F DipION, is the managing director of Nutri-Link Ltd (www.nutri-linkltd.co.uk), and editor of the clinical education website www.nleducation.co.uk. He is an Osteopath, Naturopath and Clinical Nutritionist with more than 25 years experience founding and then running a large, successful integrated medicine clinic. In addition he is a researcher and lecturer as well as an entrepreneur focused on health related business development. He was the first UK host of the Institute for Functional Medicine's 5-day intensive Applying Functional Medicine in Clinical Practice™.

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