

thelial cells and connective tissue, allow forward propulsion of lymph through the system.⁵ Ogata *et al.*⁴ observed a striking change in the collecting lymphatic wall in patients with chronic lymphoedema, with a markedly thickened smooth muscle layer, increased collagen deposition and apparent invasion of smooth muscle cells into the intimal layer. In cases of more severe lymphoedema, stenosis or 'lymphaticosclerosis' of the lymphatic lumen due to overgrowth of lymphatic smooth muscle cells was apparent. In addition, labelling of the myosin heavy chain isoforms SM1 and SM2 was reduced in lymphatic smooth muscle, and transmission electron microscopy revealed an increase in synthetic organelles, such as sarcoplasmic reticulum and Golgi complex, while contractile myofilaments were reduced.⁴ Collectively, these findings suggest that the progression of surgery-induced lymphatic injury into lymphoedema involves re-entry of lymphatic smooth muscle cells into a proliferative stage to respond to the injury, followed by their failure to mature and remodel appropriately. This change in the phenotype of lymphatic smooth muscle is akin to a common problem with angioplasty: restenosis of the lumen after plaque removal due to the synthetic vascular smooth muscle phenotype.⁶

Several studies in recent years have identified various gene mutations that contribute either to primary (inherited) lymphoedema or facilitate the development of secondary lymphoedema. Most of these identified mutations affect the lymphatic endothelium and intraluminal valve structure.^{7–9} The current finding of altered lymphatic smooth muscle phenotypes associated with secondary lymphoedema prompts the hypothesis that gene mutations that affect lymphatic smooth muscle, particularly those that control the contractile vs. synthetic phenotype, may also contribute to lymphoedema progression. These new findings may provide an explanation for the wide variability in severity of lymphoedema in patients who undergo lymph node removal.

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Conflicts of interest

None declared.

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References

- 1 Rockson SG. The unique biology of lymphatic edema. *Lymphat Res Biol* 2009; **7**:97–100.
- 2 Rockson SG. Current concepts and future directions in the diagnosis and management of lymphatic vascular disease. *Vasc Med* 2010; **15**:223–31.
- 3 Baker A, Semple JL, Moore S *et al.* Lymphatic function is impaired following irradiation of a single lymph node. *Lymphat Res Biol* 2014; **12**:76–88.
- 4 Ogata F, Fujii K, Koshim I *et al.* Phenotypic modulation of smooth muscle cells in lymphoedema. *Br J Dermatol* 2015; **172**:1286–93.
- 5 Breslin JW. Mechanical forces and lymphatic transport. *Microvasc Res* 2014; **96**:46–54.
- 6 Bennett MR. In-stent stenosis: pathology and implications for the development of drug eluting stents. *Heart* 2003; **89**:218–24.
- 7 Ferrell RE, Kimak MA, Lawrence EC *et al.* Candidate gene analysis in primary lymphedema. *Lymphat Res Biol* 2008; **6**:69–76.
- 8 Finegold DN, Kimak MA, Lawrence EC *et al.* Truncating mutations in FOXC2 cause multiple lymphedema syndromes. *Hum Mol Genet* 2001; **10**:1185–9.
- 9 Karkkainen MJ, Ferrell RE, Lawrence EC *et al.* Missense mutations interfere with VEGFR-3 signalling in primary lymphoedema. *Nat Genet* 2000; **25**:153–9.

The role of increased T helper cell 2 cytokine expression in skin weals of chronic spontaneous urticaria: are they always activating cytokines?

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ORIGINAL ARTICLE, p 1294

Interleukin (IL)-33, IL-25 and thymic stromal lymphopoietin (TSLP) are produced by epithelial and endothelial cells, thus promoting a wide range of T helper cell (Th)2-type adaptive responses. Of these, mast cell activation and degranulation, T-lymphocyte proliferation and the increased antigen-presenting properties of dendritic cells are the most reported. Increased expression and production of IL-33, IL-25 and TSLP were also shown to be responsible, in part, for the development of inflammatory diseases such as airway allergic diseases, atopic dermatitis and inflammatory bowel diseases.¹

In this issue of the *BJD*, Kay *et al.*² describe elegantly the increased expression of IL-33, IL-25 and TSLP in skin weals of patients with chronic spontaneous urticaria. This strengthens the assumption that these cytokines are indeed involved in the mechanisms of skin wealing, namely mast cell activation, degranulation and vascular leakage. Focusing on IL-33 one might notice that it presents a wide spectrum of activating abilities on cells such as fibroblasts, macrophages, lymphocytes and mast cells. However, the issue of its dual role, namely its proinflammatory effects in some diseases and its regulatory/suppressive properties in others, requires further attention (Fig. 1).

Recent studies in humans have described high levels of IL-33 in inflamed lesions of patients with inflammatory bowel disease, suggesting a regulatory role for this cytokine in disease pathogenesis. In the intestine, both protective and

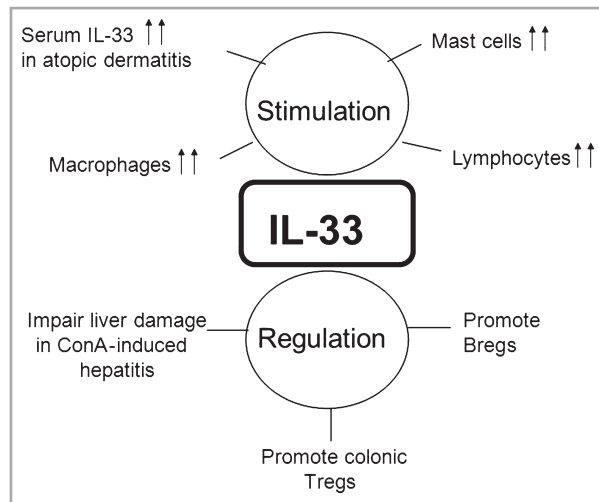


Fig 1. Interleukin (IL)-33 has a dual function. It stimulates mast cells, macrophages and lymphocytes. Increased serum levels of IL-33 are found to be associated with severe atopic dermatitis. On the other hand it suppresses liver damage in ConA-induced hepatitis and promotes both T regulatory cells (Tregs) and B regulatory cells (Bregs).

pathological roles for IL-33 have been described in murine models of acute colitis. The protective role of IL-33 was demonstrated by showing that the IL-33 receptor ST2 is preferentially expressed on colonic T regulatory cells (Tregs), were it promotes Treg function by enhancing the expression of transforming growth factor- β .³

The double life of IL-33 was assessed further. Peritoneal injection of IL-33 exacerbated inflammatory bowel disease in IL-10-deficient mice, whereas IL-33-treated IL-10 wild-type mice were protected from disease induction. Here, IL-33-induced CD19⁺ CD25⁺ CD1d⁺-producing IL-10 B regulatory cells (IL-33 Bregs) were identified to be the outcome of its protective action. Isolated IL-33 Bregs could suppress immune effector cell function when adoptively transferred.⁴

The IL-33/ST2 axis can promote both Th1 and Th2 immune responses, depending on the type of activated cells and cytokine network in damaged tissue. In this case, the IL-33/ST2 axis again proved to have a protective role in ConA hepatitis. Here, ST2-deficient mice had more severe hepatitis, with a dominance of Th1/Th17 inflammatory response. Pre-treatment of mice with IL-33 prevented ConA-induced liver damage through Th2 amplification.⁵ Having mentioned all of this, the Th2 cytokines IL-33, IL-25 and TSLP are still considered in most models to be proinflammatory and proallergic, which is in line with the interesting findings of Kay *et al*.

In support of this assumption is the finding of increased serum IL-33 in patients with atopic dermatitis, and in correlation with disease severity. It is suggested that IL-33 released from injured or barrier-disrupted skin may increase inflammation in atopic dermatitis.⁶ Further studies are needed in order to understand better the dual role of IL-33. Is this due to the site where IL-33 is produced, skin vs. gut? Or it is the cytokine concentration and its threshold in affected tissues?

Conflicts of interest

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References

- 1 Divekar R, Kita H. Recent advances in epithelium-derived cytokines (IL-33, IL-25, and thymic stromal lymphopoietin) and allergic inflammation. *Curr Opin Allergy Clin Immunol* 2015; **15**:98–103.
- 2 Kay AB, Clark P, Maurer M, Ying S. Elevations in T-helper-2-initiating cytokines (interleukin-33, interleukin-25 and thymic stromal lymphopoietin) in lesional skin from chronic spontaneous ('idiopathic') urticaria. *Br J Dermatol* 2015; **172**:1294–1302.
- 3 Schiering C, Krausgruber T, Chomka A *et al*. The alarmin IL-33 promotes regulatory T-cell function in the intestine. *Nature* 2014; **513**:564–568.
- 4 Sattler S, Ling GS, Xu D *et al*. IL-10-producing regulatory B cells induced by IL-33 (Breg^{IL-33}) effectively attenuate mucosal inflammatory responses in the gut. *J Autoimmun* 2014; **50**:107–122.
- 5 Milovanovic M, Volarevic V, Radosavjevic G *et al*. IL-33/ST2 axis in inflammation and immunopathology. *Immunol Res* 2012; **52**:89–99.
- 6 Tamagawa-Mineoka R, Okuzawa Y, Mauda K, Katoh N. Increased serum levels of interleukin-33 in patients with atopic dermatitis. *J Am Acad Dermatol* 2014; **70**:882–888.

Predicting adequate surgical margins for cutaneous squamous cell carcinoma with dermoscopy

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ORIGINAL ARTICLE, p 1308

In the 7th edition of the American Joint Committee on Cancer's staging manual, cutaneous squamous cell carcinoma (cSCC) was separated from other nonmelanoma skin cancers in the staging system for the first time and a new T-classification system was presented.¹ Today, classification of cSCCs as T1 or T2 depends greatly on whether or not high-risk features are present, including depth of invasion (thickness > 2 mm or Clark level $\geq$ IV), perineural invasion, location (ear or nonlabral lip) and poor histopathological differentiation.^{1,2} One of the most important high-risk features is a high histopathological grade (i.e. poor differentiation), which also seems to be an independent prognostic factor for both metastatic disease and overall survival.³ These recent findings fit well with the recommendation of excising poorly differentiated cSCCs with at least a 6-mm margin rather than a 4-mm margin.⁴