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Editorial

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Lysyl-oxidase in systemic sclerosis-associated pulmonary arterial hypertension: a future still to be written

This editorial refers to Lysyl oxidase, a possible role in systemic sclerosis associated pulmonary hypertension. A multicentre study, Vadasz *et al.*, doi:10.1093/rheumatology/kez035

The study performed by Vadasz et al. [1] published in this issue of *Rheumatology* gives some interesting insights into the typical vasculopathy in the context of systemic sclerosis (SSc). Vasculopathy is a hallmark of SSc [2]. Vascular abnormalities, including endothelial injury, vascular remodelling with neointimal hyperplasia, pericytes and vascular smooth muscle cells proliferation, capillary loss and ineffective angiogenesis are present from the early stages of the disease [2]. Despite vasculopathy being a generalized process in SSc, vascular complications other than Raynaud's phenomenon occur only in a subset of subjects [2]. The different vascular complications do not always coexist in the same patients, but the factors that influence the appearance of vascular complications in specific territories remain to be identified [2].

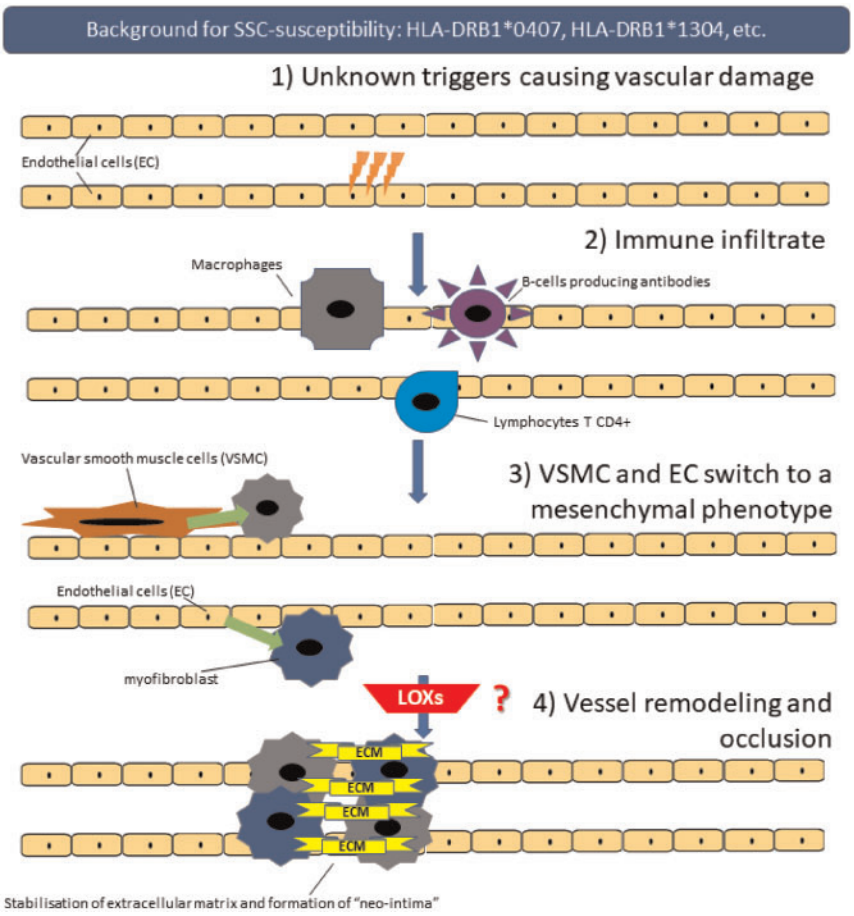
Lysyl oxidases (LOXs) are a family of five copper-dependent amine oxidases composed by LOX and four LOX-like enzymes (LOXL1-4). Enzymatic activity results in covalent crosslinking of extracellular proteins, yielding to increased tensile strength and resistance to proteolysis. LOXs play a role in several crucial physiological functions, including cell adhesion and motility, morphogenesis, maintenance of structural integrity, tissue repair, neoangiogenesis and vascular remodelling, epithelial-to-mesenchymal transition and endothelial-to-mesenchymal transition (endoMT) [3]. Moroever, LOXs favour the stabilization of atherosclerotic plaques [4], and limits aneurysm dilatation [5]. LOXs dysregulation is proposed to have a role in multiple pathological fibrotic conditions, such as liver cirrhosis, pulmonary fibrosis and heart failure, and in idiopathic pulmonary hypertension (iPAH); a condition characterised by a proliferative and obliterative remodelling of the lung vasculature.

Given the role of LOXs in fibrosis and vascular disorders, it is logical to hypothesize a dysregulation of LOXs in SSc. The multicentre study performed by *Vadasz* et al. [1] published in this issue of *Rheumatology* is the first in-depth analysis aiming to identify clinical correlates of high serum LOX in SSc. The authors studied the levels of LOX in the sera of 86 Israeli patients with established SSc, 86 Italian patients with very early SSc, 110 patients with primary Raynaud's phenomenon and 80 healthy subjects. The authors found higher serum levels of LOX in established SSc than in the other groups, although serum levels of LOX were similar in limited cutaneous (lcSSc) and diffuse cutaneous SSc (dcSSc). Interestingly, higher serum levels of LOX were associated with pulmonary hypertension as estimated by echocardiography or assessed by right heart catheterization. The authors failed to verify any relation between serum levels of LOX and other vascular or fibrotic features (such as digital ulcers, capillaroscopic pattern, heart involvement, mRSS or interstitial lung disease) as well as with disease duration or concurrent medications, with the exception of a positive correlation with disease severity as assessed by Medsger disease severity scale and a prediction of poor prognosis during follow-up. To identify the potential origin of serum LOX in SSc, the authors studied LOX expression in tissue specimens of subjects not enrolled in the first part of the study: they observed a similar LOX expression in the skin of patients with long-standing dcSSc as compared with controls. On the contrary, they found high LOX expression in lungs with SSc-associated PAH (SSc-APAH) and in a case of SSc-associated interstitial lung disease. Confocal immunofluorescence of lung specimens revealed predominant LOX expression in the remodelled vasculature. The authors propose that lung involvement, and SSc-APAH in particular, is an important source of LOX expression in SSc. Unfortunately, prospective serum sampling was not available, thus limiting the power of the analysis in the identification of other clinical correlates of high serum LOX.

In summary, the study raises the possibility that LOXs might be involved not only in immune-related fibrosis but also in vasculopathy, and might represent a link between vasculopathy and tissue fibrosis in SSc (see Fig. 1). The mechanisms remain to be understood, although it should be rational to hypothesise a role for EndoMT, a process induced by LOXs by which endothelial cells transdifferentiate to acquire mesenchymal properties, which applies to both fibrosis and vasculopathy in SSc [6].

Further studies are required to verify if LOXs could represent valuable disease biomarkers and important therapeutic targets to limit fibrosis and vascular remodelling without affecting SSc immune dysregulation. Future research should address several questions, including: (i) the relative contribution of the LOX and the different LOXL molecules and propeptides to fibrosis and vasculopathy; (ii) the relationship between plasma levels and tissue expression of the different LOXs; (iii) the dissection of whether LOX activity is particularly relevant in

Fig. 1 Lysyl oxidases as a possible link between fibrosis and vasculopathy



EC: endothelial cells; VSMC: vascular smooth muscle cells; LOXs: lysil oxydases; ECM: extracellular matrix.

specific disease phases—such as during the early phase of fibrosis establishment—that might represent a window of opportunity for targeted therapies; and (iv) the possibility of differentially modulating the pathogenic *Vs* protective activities of LOXs by targeting specific LOX isoforms in a specific temporal and/or spatial window.

SSc-APAH dramatically impacts the prognosis of patients affected by SSc [7]. Recent data have shown that patients with very early pulmonary vascular remodelling as assessed by a mean pulmonary pressure (mPAP) between 21–24 mmHg at rest or by exercise pulmonary hypertension (mPAP at peak exercise $\geqslant$ 30 mmHg and total pulmonary resistance >3 Wood Units), experience lower exercise capacity [8] and poorer outcomes [9]. In an effort to limit diagnostic delays, the 6th World Symposium for Pulmonary Hypertension proposed to lower the cut-off to define pulmonary hypertension from 25 to 20 mmHg of mean pulmonary pressure (mPAP) [10]. An unmet need in SSc is the identification of non-invasive biomarkers of PAH. The work performed by *Vadasz et al.* suggests that molecules involved in vascular remodelling may be used to identify biomarkers of early pulmonary vasculopathy in SSc. Future studies are required to assess whether LOXs might be relevant for this purpose.

In conclusion, the study conducted by *Vadasz* et al. [1] on LOXs addresses a rational and potentially exciting research topic in SSc. Despite promising findings, most of the work remains to be done and the future of this topic remains to be written.

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