Serum levels of lysyl oxidase-like 2 are increased in patients with dermatomyositis

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Lysyl oxidase-like 2 (LOXL2) belongs to the lysyl oxidase family, which has the ability to catalyse the oxidative deamination of lysines and hydroxylysines, thereby facilitating the cross linkage of collagen and elastin, thus providing tensile strength for the extracellular matrix (1). LOXL2 has been implicated in a wide range of cellular biological activities, such as regulating cell growth, proliferation, apoptosis, cell adhesion, and post-transcriptional modification (2). Thus, dysregulation of LOXL2 is associated with several disease conditions, such as inheritable connective tissue diseases, fibrotic disorders, and cancers (3). LOXL2 is expressed in the skin of the epidermis, dermal papillae, and dermal connective tissue (4); whether LOXL2 is implicated in dermatomyositis (DM), an autoimmune disease involving the skin and muscle, is still unknown. We conducted this study to assess the serum level of LOXL2 in DM patients.

We enrolled 30 healthy controls (mean age with standard deviation 47.7±7.5 years) and 64 DM patients diagnosed by the EULAR/ACR criteria (47.7±10.9years) who visited the Department of Rheumatology in the West China Hospital of Sichuan University between December 2019 and November 2020. Serum levels of LOXL2 were detected by human LOXL2 ELISA kit (CSB-EL013041H, CUSABIO). Spearman correlations between LOXL2 and disease activity assessed by Myositis Disease Activity Assessment Tool (MDAAT) were conducted. Among the 64 DM patients, 32 were accompanied by interstitial lung disease (ILD) diagnosed by high-resolution computed tomography. The study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the West China Hospital (no. 246 in 2019). Written informed consent was obtained by all participants.

The serum LOXL2 levels in DM patients were significantly increased compared to healthy controls (median [quartile], 89.9 [57.5-147.7] *vs*. 137.5 [89.4-263.2], p=0.0129) (Fig. 1A). Previous studies have reported that LOXL2 is involved in regulating lung fibrosis and is therefore a potential therapeutic target (5). We further assessed the serum LOXL2 levels in DM patients in the presence or absence of ILD. However, the serum LOXL2 levels in patients with DM-ILD were not significantly higher than in patients with DM-non-ILD, 130.4 (75.7-212.6) *vs*. 151.9 (107.4-367.0), p=0.0839 (Fig. 1B). Correlations between LOXL2 and disease activity showed that LOXL2 was positively correlated with skeletal disease activity in DM patients (r=0.328, p=0.008). There were no correlations between LOXL2 and muscular disease activity score (r=0.079, p=0.656),creatine kinase (r=0.295, p=0.09), or muscle strength (r=-0.105, p=0.554).

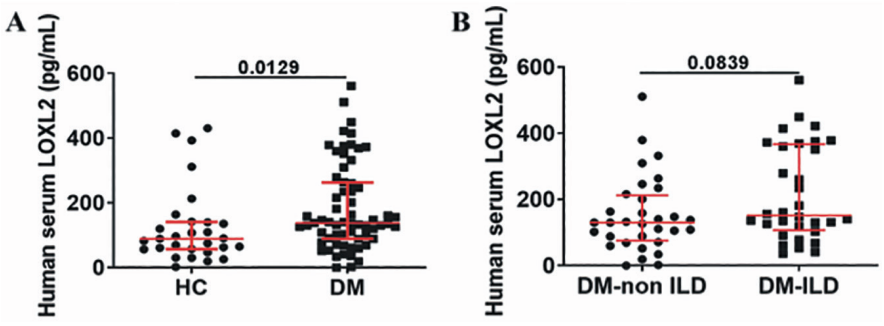

Fig. 1. Serum LOXL2 levels in dermatomyositis (DM) patients.
A: Serum LOXL2 levels in healthy controls (HC) and DM patients. **B**: Serum LOXL2 levels in DM patients in the presence (DM-ILD) or absence of interstitial lung disease (DM-non ILD).

LOXL2 has been reported in a wide range of fibrotic disorders such as idiopathic pulmonary fibrosis (6), hepatic fibrosis (7), and cardiac interstitial fibrosis (8). Fu *et al*. reported that the serum LOXL2 levels in patients with rheumatoid arthritis (RA) was higher than in healthy controls, and that this might be useful as an early RA-ILD biomarker (9). Thus, LOXL2 is considered a new anti-fibrogenic treatment target (2). The mechanisms of LOXL2 in fibrosis include mediating collagen cross linkage and fibrotic matrix stabilisation (7), triggering myofibroblast transformation and migration, and promoting collagen synthesis (10). Upon stress stimulation, such as inflammation, NF-κB is activated and leads to the increased mRNA expression level of LOXL2, which activates the PI3K/AKT/mTOR/HIF-1α pathway and promotes production of TGF-β, initiating fibroblast differentiation followed by secretion of abundant α-SMA and inducing collagen deposition (8, 10). Nevertheless, our study reported no difference in serum LOXL2 levels in DM patients in the presence or absence of ILD, which may be explained by the fact that the sample size in our study was relatively small. We found that serum level of LOXL2 was higher in DM patients than in healthy controls and LOXL2 was positively associated with MDAAT skeletal disease activity while no associations are observed between LOXL2 and MDAAT muscular disease activity score, creatine kinase, or muscle strength, which may be related to the small sample size. Whether serum level of LOXL2 can be the biomarker for predicting lung fibrosis and disease activity in patients with DM need further study. In short, our studies report that serum levels of LOXL2 are elevated and have associations with skeletal disease activity.

M. Yang, *MD*
Y. Chen, *PhD*
S. Lin, *MD*
H. Liu, *MD*
Q. Xie, *PhD*

Department of Rheumatology and Immunology, West China Hospital, Sichuan University, Chengdu, China.

Please address correspondence to:
Qibing Xie,
Department of Rheumatology and Immunology, West China Hospital, Sichuan University, 37 Guoxue Lane, Chengdu 610041, China.
E-mail: xieqibing1971@163.com

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References

1. SMITH-MUNGO LI, KAGAN HM: Lysyl oxidase: properties, regulation and multiple functions in biology. *Matrix Biol* 1998; 16: 387-98. https://doi.org/10.1016/s0945-053x(98)90012-9
2. PUENTE A, FORTEA JI, CABEZAS J *et al*.: LOXL2-A new target in antifibrogenic therapy? *Int J Mol Sci* 2019; 20: 1634. https://doi.org/10.3390/ijms20071634
3. MOON HJ, FINNEY J, RONNEBAUM T, MURE M: Human lysyl oxidase-like 2. *Bioorg Chem* 2014; 57: 231-41. https://doi.org/10.1016/j.bioorg.2014.07.003
4. MOLNAR J, FONG KS, HE QP *et al*.: Structural and functional diversity of lysyl oxidase and the LOX-like proteins. *Biochim Biophys Acta* 2003; 1647: 220-4. https://doi.org/10.1016/s1570-9639(03)00053-0
5. CHEN L, LI S, LI W: LOX/LOXL in pulmonary fibrosis: potential therapeutic targets. *J Drug Target* 2019; 27: 790-6. https://doi.org/10.1080/1061186x.2018.1550649
6. CHIEN JW, RICHARDS TJ, GIBSON KF *et al*.: Serum lysyl oxidase-like 2 levels and idiopathic pulmonary fibrosis disease progression. *Eur Respir J* 2014; 43: 1430-8. https://doi.org/10.1183/09031936.00141013
7. IKENAGA N, PENG ZW, VAID KA *et al*.: Selective targeting of lysyl oxidase-like 2 (LOXL2) suppresses hepatic fibrosis progression and accelerates its reversal. *Gut* 2017; 66: 1697-708. https://doi.org/10.1136/gutjnl-2016-312473
8. ERASMUS M, SAMODIEN E: Linking LOXL2 to cardiac interstitial fibrosis. *Int J Mol Sci* 2020; 21: 5913. https://doi.org/10.3390/ijms21165913
9. FU Q, BAI Y, LIU Y, ZHOU J, ZHENG Y: The serum level and significance of lysyl oxidase-like 2 in patients with rheumatoid arthritis-associated interstitial lung disease. *Clin Rheumatol* 2018; 37: 193-8. https://doi.org/10.1007/s10067-017-3878-0
10. YANG J, SAVVATIS K, KANG JS *et al*.: Targeting LOXL2 for cardiac interstitial fibrosis and heart failure treatment. *Nat Commun* 2016; 7: 13710. https://doi.org/10.1038/ncomms13710