Exploring the role of IL-33 in COPD: One alarmin. Two distinct pathways

What are alarmin cytokines?

Alarmin cytokines are epithelial cell-derived mediators, including IL-33, TSLP, and IL-25, that can trigger immune responses in the skin and airways, particularly in conditions like allergic inflammation, asthma, and COPD[1–3]

Pre-2003

1878–1879
Description of the mast cell and eosinophil[4,5]

1968
IgE class described[6]

1986
Cloning of human IL-4 and IL-5[7,8]

2003

2003
Discovery of IL-33 protein and mRNA in human endothelial cells[9]

IL-33 is an upstream alarmin cytokine that acts as a key orchestrator of a broad spectrum of downstream mechanisms, including inflammation, tissue homeostasis, and repair[10–12]

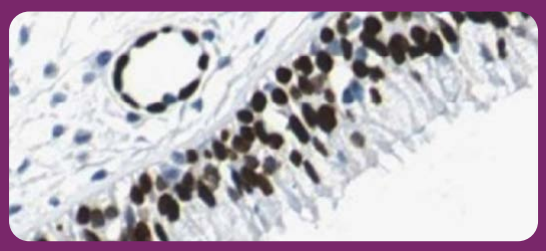
IL-33 expression in the lung

IL-33 is constitutively stored in the nuclei of structural barrier cells, including lung endothelial and epithelial cells and fibroblasts[13–17]

IL-33 expression has been shown to be increased in patients with COPD compared with healthy controls[18,19]

Necrosis and tissue injury in response to cigarette smoke, pollutants, microbes, and other stimuli trigger release of IL-33 from the cell[16,17]

IL-33 expression in epithelial and endothelial cells of normal bronchial tissue



Bronchus section stained for IL-33 (brown)
Image from Interleukin-33 (IL-33): A nuclear cytokine from the IL-1 family by Cayrol C, Girard JP. *Immunol Rev*. 2018;281(1):154-168. https://onlinelibrary.wiley.com/doi/10.1111/imr.12619. Licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

2005 — IL-33 identified as an ST2-receptor ligand[20]

2008 — IL-33 described as an alarmin[13,21]

2010 — Description of ILC2[22]

2015 — Elucidation of IL-33 OX[23]

2023 — IL-33 OX identified as a bioactive agent in RAGE/EGFR signaling[12]

IL-33 exists in two distinct bioactive forms.[12] Reduced IL-33 (IL-33 RED) is released from damaged lung tissue such as the airway epithelium and endothelium, and undergoes rapid oxidation (50% in 1–2 hours and >90% in 4 hours) and a conformational switch to oxidized IL-33 (IL-33 OX).[12,23] IL-33 RED and IL-33 OX signal via two distinct cell surface receptor complexes, activating different downstream pathways[12]

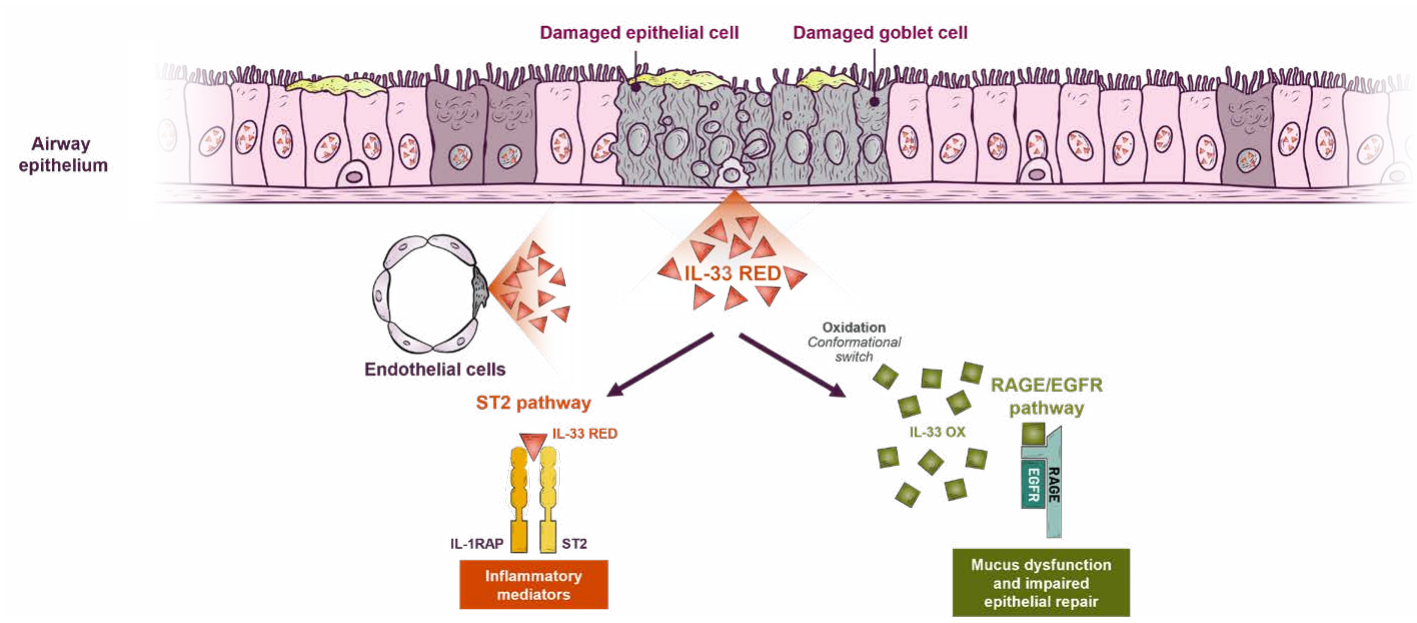
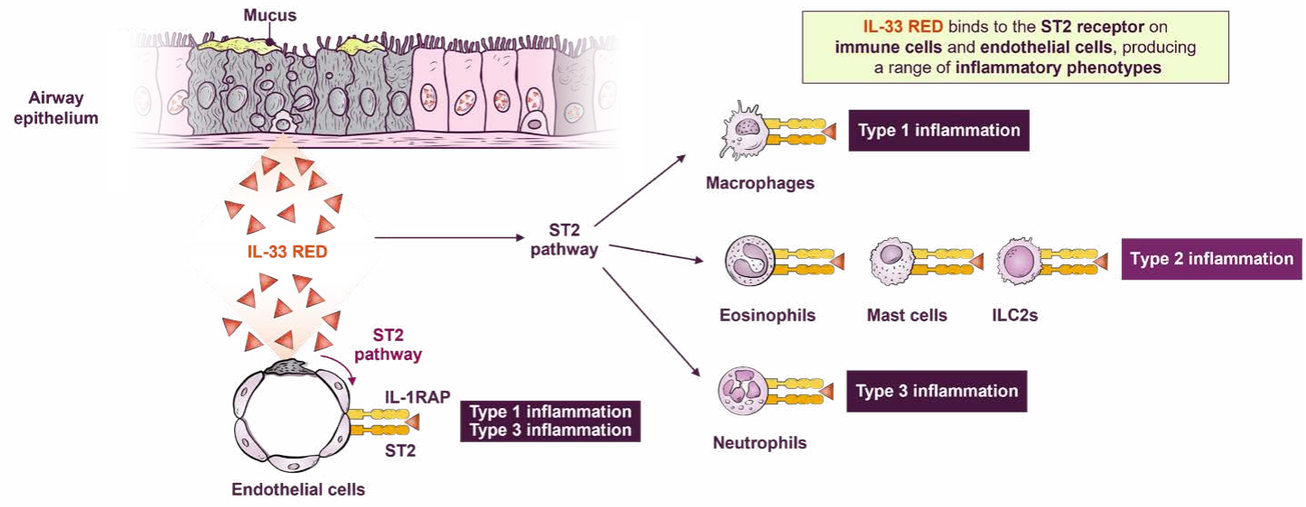


Figure adapted from Calderon AA, et al. *Eur Respir Rev*. 2023;32(167):220144; Brightling C, Greening N. *Eur Respir J*. 2019;54(2):1900651; and Strickson S, et al. *Eur Respir J*. 2023;62(3):2202210. Please note that the proposed inflammatory pathways in COPD shown here have been simplified for illustration purposes only and do not align with specific disease pathology or clinical manifestations, nor do they imply clinical benefit or relevance.

IL-33 RED binds to the ST2 receptor, which is widely expressed on the cell surface of a broad range of immune cells initiating and amplifying type 1, type 2, and type 3 inflammation[12,19,24–27]



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Multiple mechanisms can regulate IL-33 RED activity

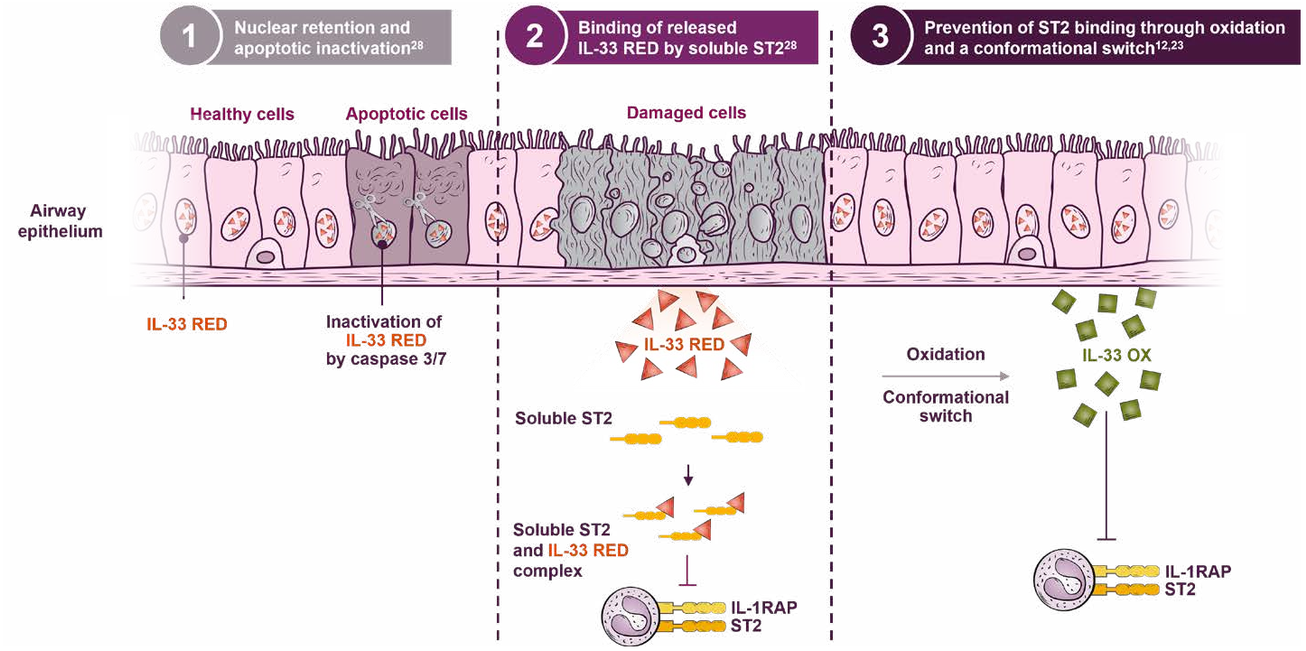


Figure adapted from Liew FY, et al. *Nat Rev Immunol*. 2016;16(11):676-689. Please note that the proposed inflammatory pathways in COPD shown here have been simplified for illustration purposes only and do not align with specific disease pathology or clinical manifestations, nor do they imply clinical benefit or relevance.

IL-33 OX can form a complex with RAGE and signal via the EGF receptor expressed on the airway epithelium.[12] This may lead to airway epithelial dysfunction and mucus hypersecretion, resulting in impaired epithelial defense and repair functions[12]

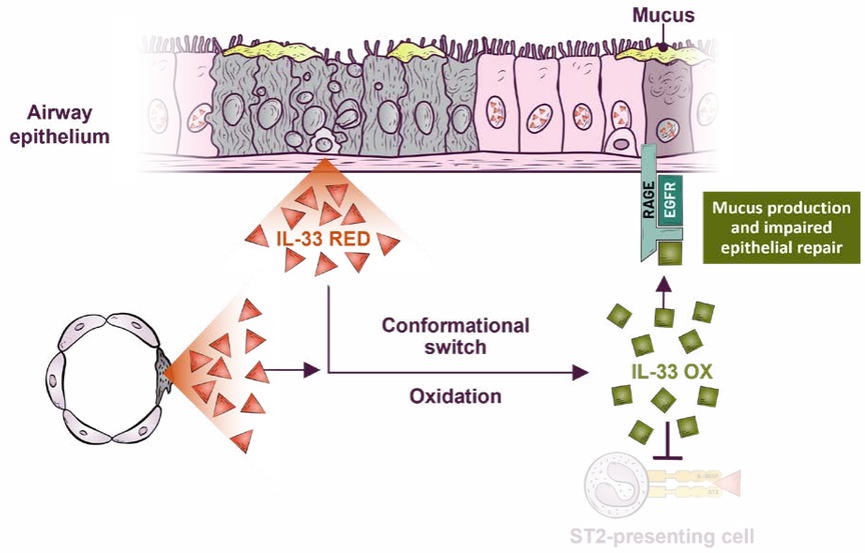
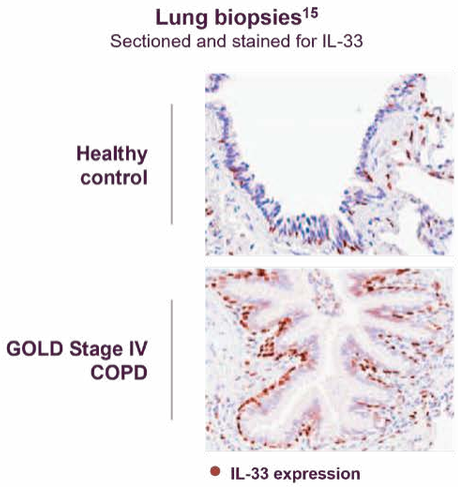
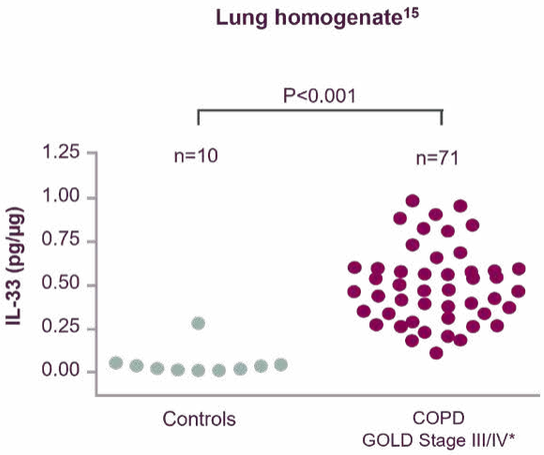


Figure adapted from Calderon AA, et al. *Eur Respir Rev*. 2023;32(167):220144 and Strickson S, et al. *Eur Respir J*. 2023;62(3):2202210. Please note that the proposed inflammatory pathways in COPD shown here have been simplified for illustration purposes only and do not align with specific disease pathology or clinical manifestations, nor do they imply clinical benefit or relevance.

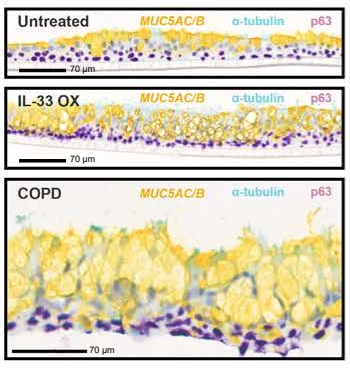
IL-33 levels increase with COPD severity (GOLD stage)[15,18,29]



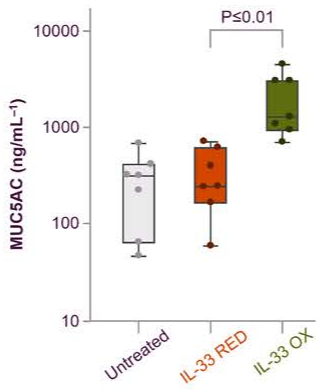


Lung biopsy images used with permission of Elsevier Inc, from Cigarette Smoke Silences Innate Lymphoid Cell Function and Facilitates an Exacerbated Type I Interleukin-33-Dependent Response to Infection by Kearley J, et al. *Immunity*. 2015;42(3):566-579; permission conveyed through Copyright Clearance Center, Inc. License number: 6207030881677.
*This cohort comprised 17 GOLD Stage III and 54 Stage IV patients with COPD.

IL-33 OX has been associated with an epithelial mucin hypersecretion phenotype[12]

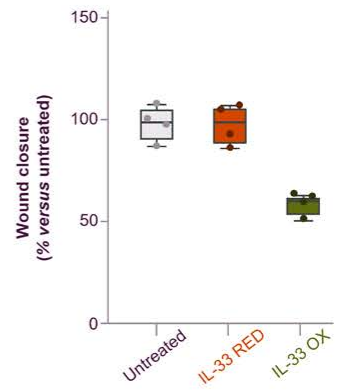


Representative immunohistochemistry of healthy bronchial air-liquid interface cultures following a 7-day treatment with 30 ng/mL^{-1} of IL-33 OX or untreated control; and representative immunohistochemistry of COPD bronchial epithelial air-liquid interface.



ELISA of MUC5AC secreted into the apical region of healthy bronchial air-liquid interface cultures stimulated with IL-33 RED, IL-33 OX, or untreated control.

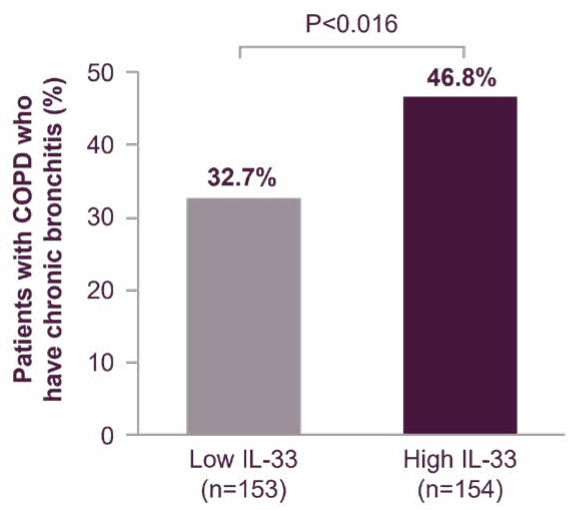
In an airway epithelium wound model, IL-33 OX, but not IL-33 RED, has been associated with impaired epithelial repair[12]

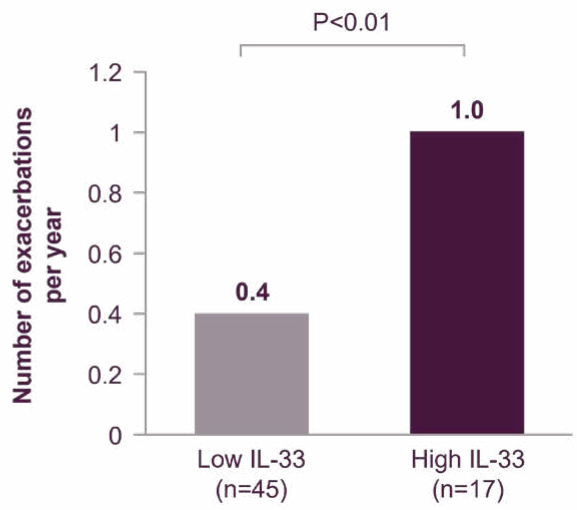


Percentage wound closure in submerged NHBE cells at 24 hours following treatment with IL-33 RED or IL-33 OX versus untreated control.

Figures from Oxidized IL-33 drives COPD epithelial pathogenesis via ST2-independent RAGE/EGFR signalling complex by Strickson S, et al. *Eur Respir J*. 2023;62(3):2202210. https://publications.ersnet.org/content/erj/62/3/2202210. Licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Increased levels of circulating IL-33 in patients with COPD are associated with chronic bronchitis[30*†] and exacerbations[18‡§]





*This study defined chronic bronchitis as phlegm for ≥3 months per year;[30] †In this analysis of 307 patients from the COPD Korean Obstructive Lung Disease cohort, IL-33 levels above the median IL-33 level of the cohort were defined as high, with all values below the median defined as low. At baseline, the median IL-33 level was 11.9 pg/mL (interquartile range 7.9–30.6);[30] ‡In this analysis of 62 patients with COPD based in Korea, levels of IL-33 in the upper quartile of the cohort were defined as high, with all levels below this value defined as low. Patients were prospectively followed for 1 year and monitored for exacerbation;[18] §Number of exacerbations per year (±SD): Low IL-33 group = 0.40 (±0.62) and High IL-33 group = 1.00 (±1.16).[18]

Key takeaway

IL-33 can drive inflammation and mucus and epithelial dysfunction via two distinct forms: IL-33 RED and IL-33 OX[12,23,27]

To connect with an MSL and learn more about IL-33, please scan the QR code or click the link below:

https://medicalinformation.astrazeneca-us.com/home/connect-with-msl.html

To unpack the burden of IL-33 in COPD and further explore the dual pathways of IL-33 RED and IL-33 OX, please scan the QR code or click the link below:

https://www.dualcopdburden.com/

COPD, chronic obstructive pulmonary disease; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ELISA, enzyme-linked immunosorbent assay; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IgE, immunoglobulin E; IL, interleukin; IL-1RAP, interleukin-1 receptor accessory protein; IL-33 OX, oxidized interleukin-33; IL-33 RED, reduced interleukin-33; ILC2, type 2 innate lymphoid cell; mRNA, messenger ribonucleic acid; MSL, medical science liaison; MUC5AC/B, Mucin-5 AC/B; RAGE, receptor for advanced glycation end products; ST2, serum stimulation-2; TSLP, thymic stromal lymphopoietin.

1. Gauvreau GM, et al. *Allergy*. 2023;78(2):402-417; 2. Roan F, et al. *J Clin Invest*. 2019;129(4):1441-1451; 3. Duchesne M, et al. *Front Immunol*. 2022;13:975914; 4. Steiner M, et al. *Biomed Res Int*. 2016;2016:8232830; 5. Varricchi G, et al. *Curr Opin Allergy Clin Immunol*. 2016;16(2):186-200; 6. Johansson SGO. *J Allergy Clin Immunol*. 2016;137(6):1671-1673; 7. Yokota T, et al. *Proc Natl Acad Sci U S A*. 1986;83(16):5894-5898; 8. Azuma C, et al. *Nucleic Acids Res*. 1986;14(22):9149-9158; 9. Baekkevold ES, et al. *Am J Pathol*. 2003;163(1):69-79; 10. Drake LY, Kita H. *Immunol Rev*. 2017;278(1):173-184; 11. Pelaia C. *ERJ Open Res*. 2024;10(5):00433-2024; 12. Strickson S, et al. *Eur Respir J*. 2023;62(3):2202210; 13. Moussion C, et al. *PLoS One*. 2008;3(10):e3331; 14. Cayrol C, Girard JP. *Cytokine*. 2022;156:155891; 15. Kearley J, et al. *Immunity*. 2015;42(3):566-579; 16. Calderon AA, et al. *Eur Respir Rev*. 2023;32(167):220144; 17. López-Rodríguez JC, et al. *J Investig Allergol Clin Immunol*. 2017;27(6):346-355; 18. Joo H, et al. *BMC Pulm Med*. 2021;21(1):86; 19. Zhou Y, et al. *J Transl Med*. 2023;21(1):902; 20. Schmitz J, et al. *Immunity*. 2005;23(5):479-490; 21. Cayrol C, Girard JP. *Proc Natl Acad Sci U S A*. 2009;106(22):9021-9026; 22. Kobayashi T, et al. *Int Immunol*. 2021;33(12):705-709; 23. Cohen ES, et al. *Nat Commun*. 2015;6:8327; 24. Riera-Martínez L, et al. *Int J Mol Sci*. 2023;24(10):8702; 25. Cai T, et al. *J Allergy Clin Immunol*. 2019;143(1):229-244.e9; 26. Vasanthakumar A, Kallies A. *Cold Spring Harb Perspect Biol*. 2019;11(3):a028506; 27. Brightling C, Greening N. *Eur Respir J*. 2019;54(2):1900651; 28. Liew FY, et al. *Nat Rev Immunol*. 2016;16(11):676-689; 29. Abdo M, et al. *Eur Respir J*. 2024;64(3):2400347; 30. Kim SW, et al. *Int J Chron Obstruct Pulmon Dis*. 2017;12:395-402.

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