Immune aging

https://doi.org/10.1038/s43587-023-00439-5

'Lnc-ing' T_{reg} cells to the aging liver

Yonghe Ma & Haiming Cao

Li and colleagues address the effect of regulatory T (T_{reg}) cells on the aging process and the role of long non-coding RNAs in T_{reg} cell function. They show that a T_{reg} cell-specific and age-induced long non-coding RNA, Altre, protects the aging liver from age-related apoptosis and metabolic abnormalities.

Aging is associated with marked changes in immunity. Age-induced decline in immune function (known as 'immunosenescence'[1]) has become common knowledge in the post COVID-19 era. Aging also causes chronic low-grade inflammation – often termed inflammaging[2] – that contributes to the development of metabolic diseases in older adults. In recent years, regulatory T (T_{reg}) cells and long non-coding RNAs (lncRNAs) have emerged as two important regulatory elements of the immune system at cellular and molecular levels, respectively. The effect of T_{reg} cell function on the aging process and the role of lncRNAs in T_{reg} cells, however, are poorly understood. In this issue of *Nature Aging*, Li and colleagues[3] simultaneously addressed both questions by delineating an aging-induced, T_{reg} cell-expressed lncRNA, which they name Altre (for 'aging liver T_{reg}-expressed non-protein-coding RNA'). They demonstrated that Altre has an important role in maintaining the immune-repressive hemostasis of T_{reg} cells in the aging liver and protects that liver from developing age-related pathologies. This work supports the vital role of liver-localized T_{reg} cells in preventing inflammaging and highlights the potential of T_{reg} cell-specific lncRNAs as therapeutic targets in age-related liver disorders.

T_{reg} cells are a unique type of T lymphocyte and function as potent regulators of immune responses by suppressing hyperstimulation or autoreactivity of the immune system[4]. LncRNAs are transcripts that are at least 200-nt long and have no predicted coding potential. Currently, over 60,000 lncRNAs – or three times the total number of protein-coding genes – have been identified[5,6], and lncRNAs have been shown to have widespread roles in cell biology and physiology[7]. The authors started their work by performing a careful screen of lncRNAs that were specifically expressed in T_{reg} cells and correlated with aging processes. It is currently unknown what fraction of the vast number of lncRNAs are functional. Furthermore, unlike protein-coding genes, the sequence–function relationship of lncRNAs is poorly understood and it is difficult to use sequence features to place lncRNAs in a biological context. Currently, one of the few proven methods to identify functional lncRNAs is to use information on how they are regulated to connect them to specific functions, but it is often necessary to overlap multiple datasets of similar regulations to identify high-confidence 'hits'[8,9]. That is exactly what these authors did. They overlapped three lncRNAs datasets to identify two lncRNAs that could have functional roles in T_{reg} cells during the aging process; only one showed expressional change with aging by experimental validation. The authors named this lncRNA Altre and demonstrated it is highly enriched in the nucleus and shows no protein-coding potential.

To study the physiological role of Altre in T_{reg} cells, the authors generated two sets of Altre-knockout mice. They first generated mice in which Altre was conditionally knocked out in T cells, and found

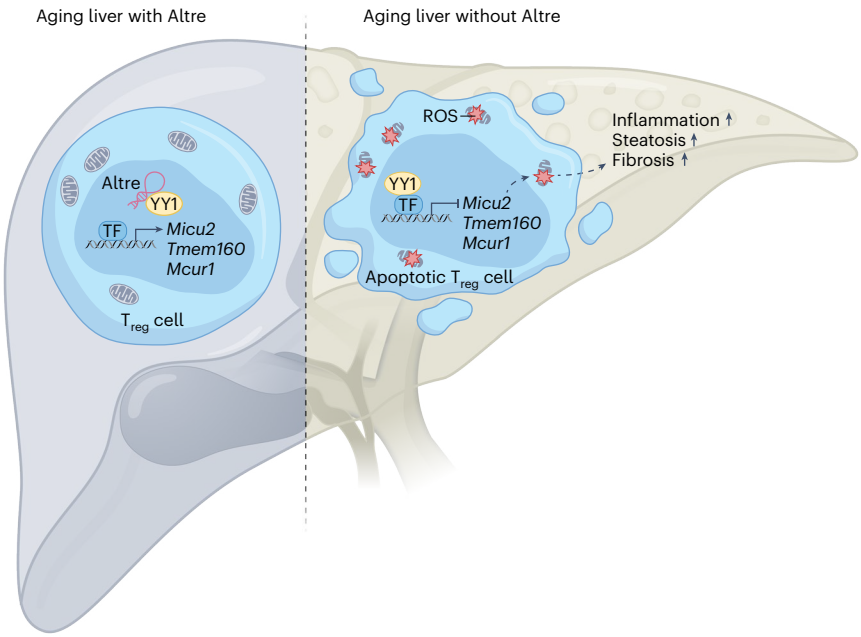

Fig. 1 | Altre maintains immune-metabolic homeostasis in the aging liver by interacting with YY1 to regulate mitochondrial-related gene expression. Induced by aging, nucleus-localized Altre sequesters YY1 (a corepressor that interferes with transcription factor (TF) binding to the promoters of genes in regulating normal mitochondrial physiology (for example, *Micu2*, *Tmem160* and *Mcur1*)), thus sustaining mitochondrial integrity (left). When Altre is depleted, YY1 is released and binds to the promoters. As a result, the transcription of mitochondrial genes is repressed, which leads to mitochondrial reactive oxygen species (ROS) production and T_{reg} cell apoptosis. Liver inflammation, steatosis and fibrosis subsequently occur, owing to the loss of immune-tolerance protection from T_{reg} cells.

no significant differences in T_{reg} cell differentiation and suppressive function or in T_{reg} cell-related pathologies in young mice. To exclude the involvement of other T cells, they subsequently generated a T_{reg} cell-specific deletion of Altre. In this model, the percentage of T_{reg} cells in the liver was normal in young mice but was significantly decreased at 14 months of age. T_{reg} cells are generated in the thymus, secondary lymphoid organs (that is, spleen and lymph node) and a range of peripheral tissues. The authors found that the reduction of the T_{reg} cell population occurred predominantly in the liver, which thus presented them with an opportunity to study the effect of T_{reg} cells (and the underlying mechanisms) on the liver aging process.

To identify the cause of the change in the liver T_{reg} cell population after Altre depletion in aging mice, the authors explored the two obvious possibilities: cell proliferation or apoptosis. They quickly excluded the former; moreover, Altre only blocked T_{reg} cell apoptosis and did not affect their suppressive functions in the microenvironment of the aged liver, which indicates that the 'quantity' — but not the 'quality' — of liver T_{reg} cells is changed in aged Altre-knockout mice.

Aging induces or potentiates an array of pathological conditions in the liver. Having found a reduced T_{reg} cell population in the aging livers of mice with T_{reg} cell-specific knockout of Altre, the authors further examined whether Altre affected liver pathogenesis during aging. They found more-severe hepatic damage and fibrosis in aged, but not in young, Altre-knockout mice. Moreover, the prolonged aging process (>18 months old) caused a higher prevalence of liver cancer and a lower survival rate in the knockout group compared with wild-type littermates. This coincided with significantly increased pro-inflammation cell subsets in aging knockout mice. The observed phenotypes are typical manifestation of inflammaging, which suggests that proper T_{reg} cell function in the aging liver is an important safeguarding mechanism against excessive activation of the immune system.

The authors also asked what mechanism is behind the T_{reg} cell apoptosis induced by Altre deletion in aged mice. By analyzing differentially expressed genes in aged groups between Altre-knockout and wild-type mice, the authors discovered substantial changes in pathways related to cellular metabolic process, T cell function and cellular response to oxidative stress. Consistent with the changes in gene expression, mitochondrial-mediated metabolic assays showed that Altre deletion in aged T_{reg} cells led to impaired mitochondrial function and metabolic perturbations and, subsequently, apoptosis. Furthermore, Altre was shown to bind to ying yang 1 (YY1), a dual-function transcriptional factor that can serve as a transcriptional activator or repressor[10]. By performing chromatin immunoprecipitation, the authors validated that Altre attenuated the binding between YY1 and the promoters of its regulated genes, particularly those involved in mitochondrial function (such as *Micu2*, *Tmem160* and *Mcur1*). This body of evidence thus supports that Altre interacts with YY1 to prevent its chromatin binding, relieving its suppression on a group of mitochondrial gene expressions. On the contrary, deletion of Altre led to enhanced YY1 binding to the promoters and reduced levels of these mitochondrial genes in aged T_{reg} cells, and, eventually, to apoptosis (Fig. 1).

There are two remaining questions that arose from this study and merit further investigation. First, the relevance of Altre to human aging needs to be explored. It is known that lncRNAs are much less conserved than protein-coding genes, at least based on their primary sequence[11]. But lncRNAs might conserve their function across species independently of their sequence. For example, a pair of positionally conserved lncRNAs, which are localized in the syntenic regions of human and mouse genomes, have recently been shown to modulate immune response in both humans and mice[12]. Thus, if a homolog of Altre in humans exists then how it functions needs to be carefully studied. In addition, the authors imply that Altre could be a therapeutic target for age-related pathologies based on the protective role of Altre, but the potential risk of enhancing Altre function needs to be first excluded. Based on the study, it is anticipated that further activating Altre would increase the T_{reg} cell population in the liver of aging mice. As the immunity of the liver is an important part of the entire defense system against pathogens, the downsides of an increased T_{reg} cell population and reduced immunity in the liver — however slight they might be — need to be examined. More specifically, it needs to be ascertained whether, under conditions in which the immune system is challenged, activation of Altre causes oversuppression of the immune response and thus immunodeficiency. It is comforting that the authors have shown that Altre-knockout mice show no negative effect on immune function, but the effect of increased Altre expression or function in young and aging mice also needs to be investigated.

The role of lncRNAs in T_{reg} cells and the influence of T_{reg} cells on the aging process are both important questions. This study provides an intriguing proof-of concept example that a T_{reg} cell-specific lncRNA can serve as a safeguarding mechanism against inflammaging and age-related metabolic abnormalities, which could open up avenues to understand and remedy aging-induced pathologies.

Yonghe Ma & Haiming Cao ✉
Cardiovascular Branch, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA.
✉e-mail: haiming.cao@nih.gov

Published online: 8 June 2023

References

1. Nikolich-Žugich, J. *Nat. Immunol.* **19**, 10–19 (2018).
2. Franceschi, C. et al. *Ann. NY Acad. Sci.* **908**, 244–254 (2000).
3. Ding, C. et al. *Nat. Aging* https://doi.org/10.1038/s43587-023-00428-8 (2023).
4. Sakaguchi, S. *Annu. Rev. Immunol.* **22**, 531–562 (2004).
5. Seifuddin, F. et al. *Sci. Data* **7**, 326 (2020).
6. Iyer, M. K. et al. *Nat. Genet.* **47**, 199–208 (2015).
7. Statello, L., Guo, C. J., Chen, L. L. & Huarte, M. *Nat. Rev. Mol. Cell Biol.* **22**, 96–118 (2021).
8. Ruan, X. et al. *Nat. Commun.* **11**, 45 (2020).
9. Ruan, X. et al. *J. Clin. Invest.* **131**, e136336 (2021).
10. Shi, Y., Lee, J. S. & Galvin, K. M. *Biochim. Biophys. Acta* **1332**, F49–F66 (1997).
11. Necsulea, A. et al. *Nature* **505**, 635–640 (2014).
12. Vollmers, A. C. et al. *Proc. Natl Acad. Sci. USA* **118**, e2016648118 (2021).

Competing interests

The authors declare no competing interests.