Metabolism Open 22 (2024) 100276

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.sciencedirect.com/journal/metabolism-open

Hydrogen sulfide derived from apoptotic cells supports immune homeostasis

In the latest issue of *Cell Metabolism*, Songtao Shi's group reveal that apoptosis is responsible for maintaining the homeostasis of hydrogen sulfide (H2S) in the body. It does so by restraining the abnormal activation of Th17 cell via sulfhydration of selenoprotein F (Sep15) [1].

Apoptosis is a type of programmed cell death, with approximately 50–70 billion cells undergoing apoptosis each day [2]. In recent years, several experimental results have clarified that apoptosis is related to autoimmune diseases, such as systemic lupus erythematosus (SLE) [3]. Apoptotic vesicles (apoVs), released by apoptotic cells, contain many components, including DNA, RNA, and proteins, which play a role in immune modulation and the promotion of cell regeneration [4]. Additionally, apoVs can also transmit metabolites to target cells and organs [5].

Hydrogen sulfide (H2S), considered a gasotransmitter, has the ability to freely penetrate cell membranes and signal specific cellular targets [6]. H2S is a natural buffer for the immune system, and its deficiency can lead to significant immune disorders [7]. H2S is generated within apoptotic cells by H2S-generating enzymes and exerts its physiological function through sulfhydration modification, a novel post-translational modification involved in multiple pathophysiological processes, including cell survival/death, differentiation, proliferation/hypertrophy, lipid metabolism, and others [8]. In 2015, Songtao Shi's team published a paper in the journal *Immunity*, revealing the importance of endogenous H2S in maintaining immune balance and its connection to immune diseases related to T cells [9]. Given that both apoptosis defects and H2S deficiency can cause severe immune disorders, it suggests a possible link between the apoptosis process and the production of endogenous H2S. More recently, Songtao Shi's team discovered that the

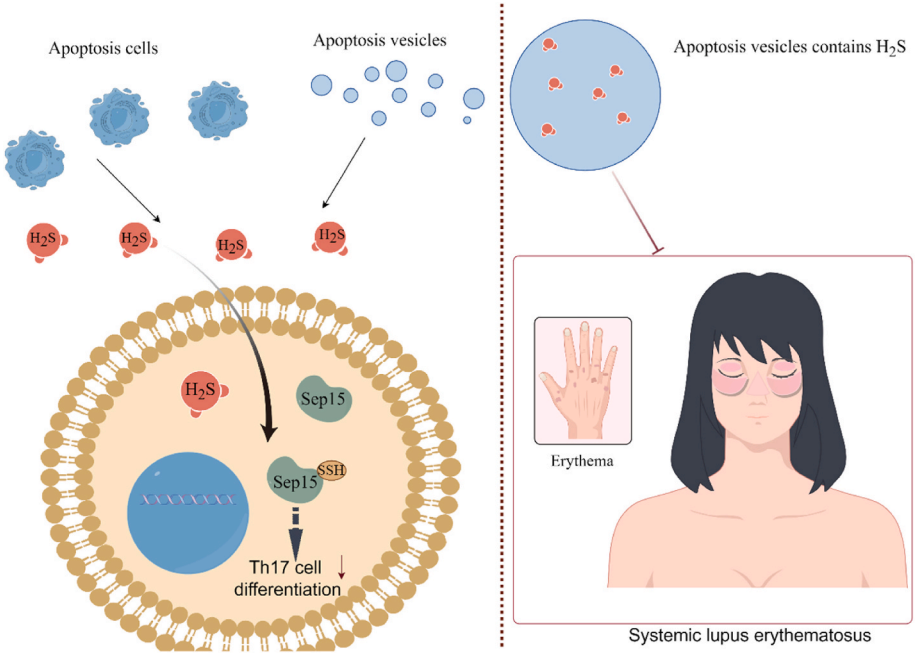

Fig. 1. H2S, derived from apoptotic cell, supports immune homeostasis. Apoptotic cells are considered vital reservoirs that produce endogenous H2S. This molecule exerts inhibitory effects on aberrant Th17 cell differentiation through sulfhydration, thereby mitigating the risk of systemic lupus erythematosus (SLE) development. By Figdraw (http://www.figdraw.com).

https://doi.org/10.1016/j.metop.2024.100276
Received 19 February 2024; Accepted 20 February 2024
Available online 21 February 2024

decrease in H2S levels is associated with apoptosis defect. Additionally, H2S inhibits Th17 cell activation by sulfhydrating selenoprotein F at the C38 site ($Sep15^{C38}$) [1].

Cell apoptosis defects are closely linked to SLE, characterized by a notable increase in the number of Th17 cells in circulation and tissues. The infiltration of Th17 cells triggers tissue inflammation and organ damage. Inhibiting the differentiation of Th17 cells in SLE patients is a prospective approach to alleviate inflammatory damage and slow down disease progression. In their study, Shi and colleagues propose a novel concept called "apoptotic gas" production. They found that cell apoptosis serves as a significant source of endogenous H2S in the body. H2S derived from apoptotic cells can hinder the abnormal differentiation of Th17 cells by modifying key proteins through sulfhydration. Additionally, they introduce a new form of "apoptotic inheritance" for the first time. It is discovered that apoVs possess the capability to inherit the cell's ability to generate H2S. Notably, apoVs may offer another practicable way to treat SLE and provide a new perspective on clinical treatments. This research is promising and may have significant implications in clinical medicine (Fig. 1).

CRediT authorship contribution statement

Ying Xu: Conceptualization, Writing – original draft. **Suzhen Chen:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Junli Liu:** Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing.

References

[1] Ou Q, Qiao X, Li Z, Niu L, Lei F, Cheng R, et al. Apoptosis releases hydrogen sulfide to inhibit Th17 cell differentiation. Cell Metabol 2024;36(1):78–89.e5.
[2] Medina CB, Mehrotra P, Arandjelovic S, Perry JSA, Guo Y, Morioka S, et al. Metabolites released from apoptotic cells act as tissue messengers. Nature 2020;580(7801):130–5.
[3] Meyer Zu Horste G, Przybylski D, Schramm MA, Wang C, Schnell A, Lee Y, et al. Fas promotes T helper 17 cell differentiation and inhibits T helper 1 cell development by binding and sequestering transcription factor STAT1. Immunity 2018;48(3). 556-69.e7.
[4] Tang H, Luo H, Zhang Z, Yang D. Mesenchymal stem cell-derived apoptotic bodies: biological functions and therapeutic potential. Cells 2022;11(23).
[5] Qu Y, He Y, Meng B, Zhang X, Ding J, Kou X, et al. Apoptotic vesicles inherit SOX2 from pluripotent stem cells to accelerate wound healing by energizing mesenchymal stem cells. Acta Biomater 2022;149:258–72.
[6] Sun F, Luo JH, Yue TT, Wang FX, Yang CL, Zhang S, et al. The role of hydrogen sulphide signalling in macrophage activation. Immunology 2021;162(1):3–10.
[7] Dilek N, Papapetropoulos A, Toliver-Kinsky T, Szabo C. Hydrogen sulfide: an endogenous regulator of the immune system. Pharmacol Res 2020;161:105119.
[8] Mantle D, Yang G. Hydrogen sulfide and metal interaction: the pathophysiological implications. Mol Cell Biochem 2022;477(9):2235–48.
[9] Yang R, Qu C, Zhou Y, Konkel JE, Shi S, Liu Y, et al. Hydrogen sulfide promotes Tet1- and tet2-mediated Foxp3 demethylation to drive regulatory T cell differentiation and maintain immune homeostasis. Immunity 2015;43(2):251–63.

Ying Xu, Suzhen Chen**, Junli Liu*
Shanghai Diabetes Institute, Department of Endocrinology and Metabolism, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

* Corresponding author.

** Corresponding author.
E-mail addresses: cszdream@163.com (S. Chen), liujunli@sjtu.edu.cn (J. Liu).