



Low-input Proteomics Reshapes Our Understanding of Regulatory Mechanisms in Early Embryonic Development*

CHEN Hong-Yu**

(CAS Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, Shanghai 200031, China)

Abstract Early mammalian embryogenesis represents a central question in life sciences, yet its molecular regulation has long been inferred primarily from transcriptomic and translomic analyses. Recently, a study by Zhu *et al.* (2025) based on low-input proteomic approaches systematically charted protein dynamics from oocytes to blastocysts in both mice and humans, further interrogating molecular signatures of developmentally compromised human embryos at the single-embryo level. This work not only substantially expands proteome coverage during early development, but also reveals a pervasive uncoupling between transcriptional activation, translational initiation, and protein accumulation. These findings provide new perspectives on the relationship between zygotic genome activation (ZGA) and lineage specification. This paper discussed the central role of low-input proteomics in this study, highlighted its implications for reshaping current paradigms of early embryonic development, and considered its potential applications across broader areas of biomedical research.

Key words low-input proteomics, early embryonic development, zygotic genome activation (ZGA), protein dynamics, single-embryo analysis

DOI: 10.3724/j.pibb.2026.0069

CSTR: 32369.14.pibb.20260069

Over the past decade, single-cell transcriptomic and low-input translomic profiling have profoundly advanced our understanding of early embryonic development. These approaches have enabled detailed characterization of transcriptional activation and translational regulation during zygotic genome activation (ZGA)^[1]. However, the direct executors of developmental processes are proteins, rather than mRNAs or ribosome-bound transcripts. Because proteins cannot be amplified, span a wide dynamic range, and are present at extremely low abundance in early embryos due to low cell numbers, systematic analyses of single embryos at the protein level have long been technically challenging^[2-4]. As a result, it remains unclear whether transcriptional or translational signals can reliably reflect functional output.

Recent advances in low-input proteomics by Zhu

et al.^[5] (2025) have made it possible to obtain deep, reproducible, and reliable protein quantification from single embryos or very limited embryonic material. The study discussed here leverages these technological developments to generate an unprecedented proteomic characterization of early human and mouse embryos. By doing so, it moves the field beyond transcriptional potential and toward direct interrogation of protein behavior during early development^[5].

* This work was supported by grants from the National Key R&D Program of China (2024YFA0916602) and the Yangfan Project of the Shanghai Science and Technology Commission (24YF2752300).

** Corresponding author.

Tel: 86-21-54921928, E-mail: hychen@ion.ac.cn

Received: February 5, 2026 Accepted: March 17, 2026

1 Systematic uncoupling between translational activation and protein accumulation

By integrating proteomic, transcriptomic, and translational datasets, the study demonstrates that in early embryos, translationally activated genes do not necessarily exhibit a concomitant increase in protein abundance (Figure 1). Instead, many proteins display

delayed accumulation or remain relatively stable despite active or silent translation. This observation indicates that protein homeostasis during early development is subject to finely tuned regulation through both synthesis and degradation. Consequently, transcriptional or translational information alone is insufficient to accurately predict functional protein output, underscoring the unique value of low-input proteomics in revealing these otherwise hidden regulatory layers.

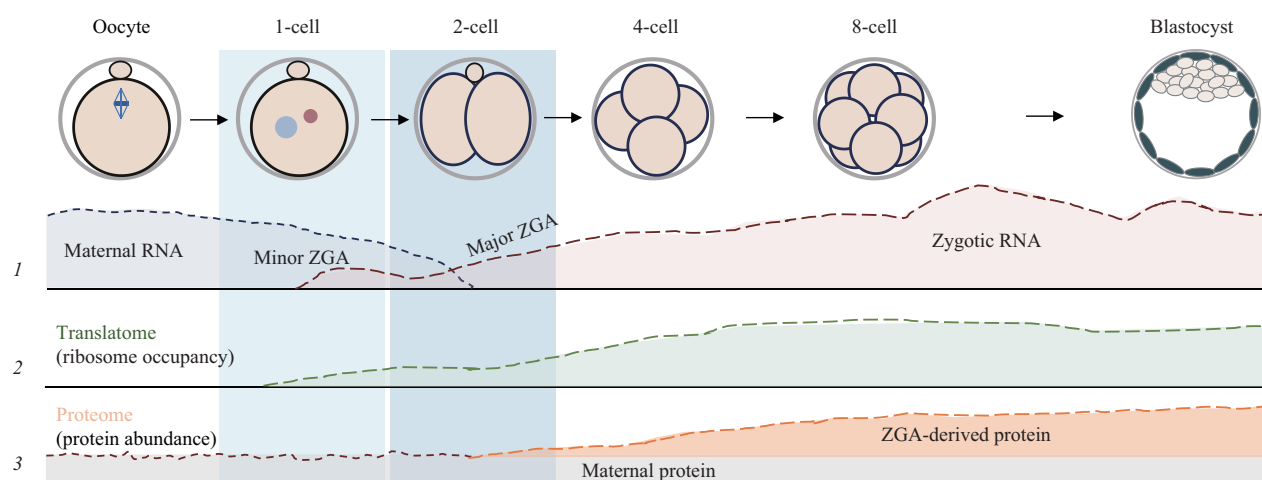


Fig. 1 Schematic illustration of molecular regulation from the oocyte to the blastocyst in mice

Layer 1 depicts the well-established transcriptional dynamics of the maternal-to-zygotic transition, including the progressive clearance of maternal RNAs and the onset of minor and major ZGA. Layer 2 represents translational engagement, reflected by ribosome occupancy, which is initiated early during ZGA but exhibits relatively modest changes across subsequent developmental stages. Layer 3 illustrates protein abundance dynamics, highlighting a delayed and progressive accumulation of proteins encoded by ZGA transcripts, together with gradual turnover of maternal proteins. Collectively, the schematic emphasizes the temporal uncoupling among transcriptional activation, translational engagement, and functional protein output, a central insight emerging from low-input proteomic analyses of early mouse embryos.

2 Redefining the functional timing of zygotic genome activation

ZGA has traditionally been viewed as a discrete developmental event dominated by transcriptional activation. Proteomic data from this study, however, suggest that protein products of many ZGA transcripts do not exert immediate functional roles. Instead, they accumulate progressively and reach functional relevance at later stages, particularly during blastocyst formation. This finding reframes ZGA as a preparatory phase that establishes a protein reservoir for subsequent lineage specification, highlighting a

multiscale temporal structure in early developmental regulation.

3 From transcriptional and translational inference to functional single-embryo heterogeneity

Using single-embryo proteomic analyses, the authors systematically characterize molecular heterogeneity among developmentally compromised embryos at the level of functional execution. Remarkably, embryos derived from the same patient exhibit substantial differences in protein regulatory states, differences that cannot be adequately explained

by transcriptional or translational inference alone. These observations demonstrate that proteomics provides direct and indispensable functional information for dissecting the molecular basis of embryonic developmental failure and its embryo-specific characteristics.

4 Open questions and future directions

Despite its conceptual and technical advances, the application of low-input proteomics raises several important questions. At the biological level, how the stability and turnover of different classes of proteins are precisely regulated in early embryos remains poorly understood. It is also unclear whether protein dynamic features become further amplified across distinct cell fates during subsequent lineage specification. In addition, the extent to which these regulatory principles are conserved across species or recapitulated in *in vitro* embryo models warrants systematic investigation.

At the same time, continued methodological improvements in low-input proteomics will be critical for addressing these questions, particularly with respect to sensitivity, quantitative accuracy, and proteome coverage. Further integration with spatially resolved and time-resolved approaches may enable more precise mapping of protein dynamics during early development. Together, advances in both biological interrogation and analytical technology will be essential for refining the molecular frameworks of early embryonic regulation.

5 Outlook: extending beyond embryonic development

From a broader perspective, the significance of low-input proteomics extends well beyond early embryogenesis. This approach holds considerable

promise for studies of stem cell differentiation, embryo-like models, rare cell populations, and early disease mechanisms. As analytical depth, throughput, and standardization continue to improve, low-input proteomics is poised to serve as a critical bridge linking gene expression information to functional biological outcomes.

6 Concluding remarks

In summary, the study discussed here uses low-input proteomics as a central analytical framework to gain new molecular insights into early mammalian embryonic development. By complementing and refining models derived primarily from transcriptomic and translatomic data, it offers a more functionally grounded view of early developmental decision-making. Additionally, it proposes a new way to understand how poor-quality embryos are formed. With continued technical refinement, proteomics is poised to play an increasingly indispensable role across diverse areas of biomedical research, much like single-cell sequencing has done over the past decade.

References

- [1] Schulz K N, Harrison M M. Mechanisms regulating zygotic genome activation. *Nat Rev Genet*, 2019, **20**(4): 221-234
- [2] Dang Y, Zhu L, Yuan P, *et al*. Functional profiling of stage-specific proteome and translational transition across human pre-implantation embryo development at a single-cell resolution. *Cell Discov*, 2023, **9**(1): 10
- [3] Ahmad R, Budnik B. A review of the current state of single-cell proteomics and future perspective. *Anal Bioanal Chem*, 2023, **415**(28): 6889-6899
- [4] Li S, Li S, Liu S, *et al*. Mass spectrometry-based solutions for single-cell proteomics. *Genom Proteom Bioinform*, 2025, **23**(1): qzaf012
- [5] Zhu W, Meng J, Li Y, *et al*. Comparative proteomic landscapes elucidate human preimplantation development and failure. *Cell*, 2025, **188**(3): 814-831.e21

低起始量（low-input）蛋白质组学推动 对早期胚胎发育调控的新认识*

陈红玉**

（中国科学院脑科学与智能技术卓越创新中心，上海 200031）

摘要 哺乳动物早期胚胎发育是生命科学研究中的核心问题之一，其分子调控机制长期以来主要依赖转录组学和翻译组学。近期，Zhu 等（2025）在《细胞》（*Cell*）发表的工作，基于低起始量（low-input）蛋白质组学技术，揭示了人类和小鼠从卵母细胞到囊胚阶段的蛋白质动态变化，并在单胚胎尺度上对发育失败人类胚胎的分子特征进行了分析。该研究不仅显著拓展了早期胚胎蛋白质组的覆盖深度，还揭示了转录激活、翻译启动与蛋白质积累之间并非简单对应的关系，为重新认识合子基因组激活（ZGA）与谱系决定之间的联系提供了新的视角。本文将围绕低起始量蛋白质组学在该研究中的关键作用，对其在推动早期胚胎发育研究范式转变中的意义进行评述，并进一步讨论其在生命科学其他研究领域中的潜在应用价值。

关键词 低起始量蛋白质组，早期胚胎发育，合子基因组激活，蛋白质动态，单胚胎分析

中图分类号 Q2-3, Q28, Q33

DOI: 10.3724/j.pibb.2026.0069

CSTR: 32369.14.pibb.20260069

* 国家重点研发计划（2024YFA0916602）和上海市扬帆专项（24YF2752300）资助。

** 通讯联系人。

Tel: 021-54921928, E-mail: hychen@ion.ac.cn

收稿日期: 2026-02-05, 接受日期: 2026-03-17