Why better single-cell data about natural oogenesis would probably help

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Brief summary

To better understand the process of reproduction mechanistically, and in particular to develop in vitro oogenesis, it helps to understand the molecular dynamics of cells involved in reproduction. A central way to understand those dynamics is, simply, rich observational data of the states of single cells as they participate in germline development.

This data (single-cell transcriptomics and epigenomics) would give us a map of what cell types there are, when and how they change, and how we can recapitulate and manipulate those changes. There has been good recent work collecting some molecular cell data on human reproduction, but more would be helpful.

Importance of in vitro oogenesis

Oogenesis involves three key processes: epigenetic resetting and imprinting, meiotic division, and a large amount of cytoplasm growth. The gold standard for understanding these processes would be to recapitulate them in vitro by directly manipulating gene regulatory signals. This level of manipulation goes beyond coaxing cells to undergo meiosis by co-culturing with natural ovary support cells, which is the main method currently used in mice. It will be much easier to achieve this if there is public data showing the detailed gene regulatory states of natural germline cells.

Achieving this gold standard would enable efficiently generating many eggs from somatic cells, and thus would:

- Provide treatment for infertility due to insufficient numbers of eggs, eggs with defects, or age-related scarcity of eggs.
- Enable couples with mismatched gametes (e.g. gay, trans) to have genetic children.
- Help women avoid expensive and painful superovulation treatments, and avoid tradeoffs around timing when to have children.
- Make it much easier to scientifically study crucial cell processes such as meiosis and epigenetic reprogramming.
- Solve the female half of the epigenomic correction problem for reprogenetics.

State of the art of natural oogenesis data

Summary

With a clearer picture of cell dynamics in developing ovaries, scientists would be better positioned to understand and recapitulate oogenesis in vitro (i.e. induce meiosis, epigenetic reprogramming, and oocyte growth). Mouse oogenesis can be recapitulated in vitro, but mainly using expensive and inefficient support methods such as reconstituted ovary-like tissues. A more efficient approach would be to use cocktails of molecules to induce meiosis, rather than relying on difficult co-cultures. Entry into meiosis I has been achieved efficiently in mouse stem cells without ovarian support cells, but the resulting germinal-vesicle oocytes are not high-quality and can't progress to meiosis II[1][2]. Meiosis has not been fully achieved in human oocyte-like cells in vitro, though entry and partial progress through prophase I have been achieved[3].

[1] Nosaka, Yoshiaki, Masahiro Nagano, Yukihiro Yabuta, et al. "Generation of Germinal-Vesicle Oocytes from Mouse Embryonic Stem Cells under an Ovarian Soma-Free Condition." Developmental Cell 60, no. 21 (2025): 2976-2994.e13. https://doi.org/10.1016/j.devcel.2025.06.008.

[2] Metacelsus. "Mouse Caviar." Substack newsletter. De Novo, July 4, 2025. https://denovo.substack.com/p/mouse-caviar.

[3] Smela, Merrick Pierson, Jessica Adams, Carl Ma, et al. "Initiation of Meiosis from Human iPSCs under Defined Conditions through Identification of Regulatory Factors." Science Advances 11, no. 33 (2025): eadu0384. https://doi.org/10.1126/sciadv.

Meiosis I starts around week 11 or 12 of fetal development, and then proceeds until arrest in late meiosis I, the dictyate stage, with some starting around weeks 16—18. To date, very roughly 125k cells from fetal ovaries around post-conception weeks 10—18 have been profiled with RNA sequencing, and most of these are not the key cells (oocytes and their direct support cells). More data would fill in gaps between time points, and would further resolve important rare cell types and transition states.

More detail: Atlases of reproductive cells

Until recently, *omic sequencing to measure proteins, RNAs, and epigenetic states of cells was done in bulk. Bulk sequencing gives an average picture of cell states in a tissue, which doesn't tell us what cell types there are and when and how cells transition between types. Cell types that are rare in tissues can't be seen this way. Oocytes make up less than 0.3% of ovarian tissue, and granulosa cells (key support for oocytes) make up less than 2%[4].

In the past decade, using new methods for parallel high-throughput single-cell sequencing, scientists have been building atlases of cells from tissues throughout the human body. This data gives precise information about cells: their subtypes, spatial distribution, precise complements of biomolecules, transitional states, differentiation trajectories, and co-regulation effects[5][6][7]. Some tissues, e.g. brain tissues, have many millions of single-cell datapoints. But reproductive tissue has received relatively less attention because reproductive science in general is underserved[8]; and fetal reproductive tissue in particular is harder to obtain.

Marečková et al. (2022) review the state of cell atlas data in human reproductive tissues (see Table 1 in the pdf)[9]:

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[4]Wagner, Magdalena, Masahito Yoshihara, Iyadh Douagi, et al. 'Single-Cell Analysis of Human Ovarian Cortex Identifies Distinct Cell Populations but No Oogonial Stem Cells'. Nature Communications 11, no. 1 (2020): 1147. https://doi.org/10.1038/s41467-020-14936-3

[5]Regev, Aviv, Sarah A Teichmann, Eric S Lander, et al. 'The Human Cell Atlas'. eLife 6 (December 2017): e27041. https://doi.org/10.7554/eLife.27041

[6]He, Shuai, Lin-He Wang, Yang Liu, et al. 'Single-Cell Transcriptome Profiling of an Adult Human Cell Atlas of 15 Major Organs'. Genome Biology 21, no. 1 (2020): 294. https://doi.org/10.1186/s13059-020-02210-0

[7]Ye, Fang, Jingjing Wang, Jiaqi Li, Yuqing Mei, and Guoji Guo. 'Mapping Cell Atlases at the Single-Cell Level'. Advanced Science 11, no. 8 (2023): 2305449. https://doi.org/10.1002/advs.202305449

[8]Mercuri, Natalie D., and Brian J. Cox. 'Meta-Research: A Poor Research Landscape Hinders the Progression of Knowledge and Treatment of Reproductive Diseases'. Preprint, bioRxiv, 19 November 2021. https://doi.org/10.1101/2021.11.16.468787

[9]Marečková, Magda, Hassan Massalha, Valentina Lorenzi, and Roser Vento-Tormo. 'Mapping Human Reproduction with Single-Cell Genomics'. Annual Review of Genomics and Human Genetics 23, no. Volume 23 (2022): 523–47. https://doi.org/10.1146/annurev-genom-120121-114415

Table 1 Key studies that profiled reproductive organs using single-cell genomics technologies, listed in chronological order from top to bottom for each tissue

Tissue analyzed	Example publications	Total cell/nucleus number[a]	Total donor number[b]	Technology[c]
Fetal gonads	Guo et al. (38)	319	6 (F), 9 (M)	scRNA-seq [Tang et al. (95)]
	Li et al. (62)	~2,100	17 (F), 12 (M)	scRNA-seq (SS2)
	Vértesy et al. (102)	73	4 (F), 1 (M)	scRNA-seq (SS2)
	Chitiashvili et al. (19)	~50,000	5 (F), 5 (M)	scRNA-seq (10x)
	Garcia-Alonso et al. (34)	~485,000	33 (F), 22 (M)	scRNA-seq, scATAC-seq, ST (Visium), Multiome (all 10x)
Postnatal testis	Guo et al. (39)	~1,300	2	scRNA-seq (10x)
	Sohni et al. (88)	~14,800	2	scRNA-seq (10x)
	Guo et al. (41)	~7,700	4	scRNA-seq (10x)
	Guo et al. (42)	~2,500	1	scRNA-seq (10x)
Adult testis	Guo et al. (40)	92	5	scRNA-seq (C1)
	Guo et al. (39)	~6,500	3	scRNA-seq (10x)
	Hermann et al. (47)	~31,000	16	scRNA-seq (10x, C1)
	Wang et al. (105)	~3,000	10	scRNA-seq (SS2)
	Sohni et al. (88)	~18,700	2	scRNA-seq (10x)
	Zhao et al. (116)	~80,000	17	scRNA-seq (10x, BD Rhapsody)
	Alfano et al. (1)	~5,000	4	scRNA-seq (10x)
	Di Persio et al. (27)	~28,600	6	scRNA-seq (10x)
	Chen et al. (17)	NA	2	ST (Slide-seqV2)
Adult ovary	Fan et al. (30)	~20,600	5	scRNA-seq (10x)
	Wagner et al. (104)	~24,300	21	scRNA-seq (10x)
	Llonch et al. (65)	66	37	scRNA-seq (SS2)
Fallopian tube	Hu et al. (50)	~5,800	15	scRNA-seq (SS2)
	Dinh et al. (28)	~53,000	8	scRNA-seq (10x)
Endometrium	Wang et al. (107)	~73,100	29	scRNA-seq (C1,10x)
	Garcia-Alonso et al. (33)	~75,900	9	scRNA-seq, snRNA-seq, ST (Visium) (all 10x)
Uterine–placental interface	Pavličev et al. (74)	86	2	scRNA-seq (C1)
	Tsang et al. (98)	~38,400	8	scRNA-seq (10x)
	Suryawanshi et al. (92)	~21,000	9	scRNA-seq (10x, DS)
	Vento-Tormo et al. (101)	~59,000	12	scRNA-seq (10x, SS2)
	Pique-Regi et al. (77)	~78,000	9	scRNA-seq (10x)

[a]Number of cells or nuclei that passed quality control and were newly profiled by the study; cells or nuclei that came from integration with previously published data sets are excluded. Abbreviation: NA, not applicable.

[b]Abbreviations: F, female; M, male.

[c]Abbreviations: 10x, various kits and kit versions available from 10x Genomics for specific applications; C1, Fluidigm C1; DS, Drop-seq; scATAC-seq, single-cell assay for transposase-accessible chromatin with sequencing; scRNA-seq, single-cell RNA sequencing; snRNA-seq, single-nucleus RNA sequencing; SS2, Smart-seq2; ST, spatial transcriptomics.

By and large, these datasets are fairly small—up to at most tens of thousands of cells or nuclei measured.

The largest dataset they list is Garcia-Alonso et al. (2022), which includes data for cells from human female fetal gonadal tissue—213k cells measured with single-cell RNA sequencing, and 84k with ATAC sequencing (a kind of epigenomic measurement)[10]. Maybe something like half their data is between weeks 10—18.

Subsequent work has continued adding to this data, though usually in small increments[11][12]. Wamaitha et al. (2023) were able to refine several points of cell lineage in reproductive tissue by collecting more data from ovary tissue (about 23k cells). (Lorenzi et al. (2026) provide a dataset with around 300k (210k from weeks 10—20) scRNAseq datapoints for human female fetal reproductive tissue, but they *exclude* gonads[13].) Lardenois et al. (2026) add about 67k female cells, but they stop at 12 weeks (and may under-collect germline

[10]Garcia-Alonso, Luz, Valentina Lorenzi, Cecilia Icoresi Mazzeo, et al. 'Single-Cell Roadmap of Human Gonadal Development'. Nature 607, no. 7919 (2022): 540–47. https://doi.org/10.1038/s41586-022-04918-4

[11]Wamaitha, Sissy E., Xichen Nie, Erica C. Pandolfi, et al. 'Single-Cell Analysis of the Developing Human Ovary Defines Distinct Insights into Ovarian Somatic and Germline Progenitors'. Developmental Cell 58, no. 20 (2023): 2097-2111.e3. https://doi.org/10.1016/j.devcel.2023.07.014

[12]Taelman, Jasin, Sylwia M. Czukiewska, Ioannis Moustakas, et al. 'Characterization of the Human Fetal Rete Region by Single Cell Transcriptional Analysis of Gonads and Mesonephros/Epididymis'. Preprint, bioRxiv, 22 July 2022. https://doi.org/10.1101/2022.07.20.500903

[13]Lorenzi, Valentina, Cecilia Icoresi-Mazzeo, Charlotte Cassie, et al. "Spatiotemporal Cellular Map of the Developing Human Reproductive Tract." Nature 650, no. 8101 (2026): 428–37. https://doi.org/10.1038/s41586-025-09875-2.

cells due to their fragility)[14]. That said, this paper produced new findings using the growing set of data, e.g. new markers and newly tracing cells (e.g. *rete* cells), which is a small illustration that this new data does keep refining our picture of cell types and dynamics.

So, there's a significant sparsity of data for female gonadal tissue from post-conception weeks 10—18, a period when germline cells and their support tissues are going through key differentiation and development. Because of the data gap, the current collection of datasets may not yet be sufficient to resolve the rare cell types and transition states that are key to understanding gametogenesis, especially meiosis and the epigenetic reset.

[14]Lardenois, Aurélie, Antonio Suglia, Chad Lewis Moore, et al. "Single-Cell Exploration of Gonadal Somatic Cell Lineage Specification during Human Sex Determination." Developmental Cell 61, no. 2 (2026): 400-415.e6. https://doi.org/10.1016/j.devcel.2025.09.011.