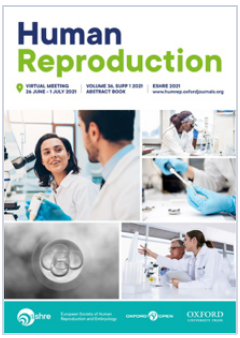

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P–458 A computational biology approach to improve in-vitro folliculogenesis

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Abstract

Study question

Considering the complexity of mechanisms involved in mammalian ovarian folliculogenesis, how about improving the current in-vitro folliculogenesis (ivF) protocols to prolong individual reproductive chance?

Summary answer

Computational modelling approach based on network theory was used to manage complexity, improve ivF knowledge and discover new molecules to be targeted for innovating assisted-reproductive-technologies. What is

known already: Over the past decades, based on the large ovarian-pool of immature-gametes availability, ivF systems were developed in several mammalian species to support oocyte growth in order to preserve human-fertility and contrast endangered species extinction. Only mouse live-births were obtained when primordial/primary follicles were cultured in-vitro, instead the oocyte differentiation is extremely slow in medium-sized mammals. Moreover, the degree of meiotic-competence is quite incomplete if compared to mice, because oocytes must proceed until late antral-follicle stage to acquire a complete developmental competence. These observations denote the importance to adopt further investigations for establishing a complete ivF protocol in translational mammal model.

Study design, size, duration

Two researchers expert on reproductive biology generated the Web of Science-Mammals-Made in-vitro folliculogenesis (WoS_MMivF) database including 1111 manuscripts published in peer-reviewed international papers indexed selected in Advanced Search of WoS "Core-collection" by carrying out an independent analysis. Two additional researchers verified the correctness of the records.

Participants/materials, setting, methods

WoS_MMivF network was built up using Cytoscape 2.6.3 software. The network was analyzed for topological parameters (closeness-centrality, betweenness-centrality and edge count) and to identify key controllers (Hub.BN). Bidimensional-kernel-density-estimation (2D KDE) identifies Hub.BN controllers; Search-Tool-for-the-Retrieval-of-Interacting-Genes/Proteins (STRING) were used to enrich the network with new proteins.

Main results and the role of chance

The analysis of topological parameters demonstrated that the network is scale-free according to Barabási-Albert-

model with a high-degree of robustness-against-random-damage, great controllability and navigability. The network reproduces a coherent framework identifying cross-talking molecules playing a key role in the inter-follicular/intra (somatic and germinal compartment) dialogue.

The network allows to organize signalling transduction events/molecules by stratifying them in three layers: input-layer recognizes molecules generating the information flux working as systemic endocrine (pituitary/chorion/enteric-related endocrine hormones) and local paracrine-factors (TGFbeta-superfamily-members and growth-factors) exerting either intrafollicular control or remote feedback on reproductive-cycle. Processing-layer presents molecules able to elaborate/amplify the endocrine/paracrine controllers of ovarian functions, including components of codified intracellular-signaling-pathways like PI3K, KIT and MAPK and second messengers cAMP and Ca2+. These cascades are necessary to promote in-vitro reproducible follicular functions and modulate steroidogenesis, representing molecular events stratified in the output-layer.

STRING analysis allowed to extend the regulatory flow of information towards two major biological action contexts: metabolic-control (paracrine-factors and signal-transduction) and angiogenesis. Metabolic-control mediated by mTOR and its interactor cognates FOXO1, FOXO3/SIRT1 plays a key role for ivF, representing the energy sensors of the reproductive cells in hypothalamic-pituitary-ovarian-axis first regulating the status of follicle quiescence/activation and then fate of the structure (specialization or apoptosis).

Limitations, reasons for caution

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Wider implications of the findings: STRING identified mTOR as key pathway of folliculogenesis, which might act as a molecular-switch to be pharmacologically targeted for potential new in-vitro strategies modulating follicular fate. These results suggest that computational approach in biology might offer perspective in identifying unknown signals, implementing research questions and innovative protocols to face female-fertility.

Trial registration number

Not applicable

Topic: angiogenesis, apoptosis, signal transduction, transforming growth factor beta, computational biology, fertilization in vitro, hormones, 1-phosphatidylinositol 3-kinase, chorion, computer simulation, extinction, psychological, feedback, fertility, genes, germ cells, growth factor, hair follicle, mammals, mitogen-activated protein kinases, oocytes, ovarian follicle, peer review, reproductive physiological process, reproductive techniques, assisted, second messenger systems, software, cyclic amp, mice, pituitary gland, secondary follicle of ovary, steroidogenesis, folliculogenesis, live birth, paracrine, intracellular signaling cascade, phosphoinositide 3-kinase, calcium ions, ovarian function, mtor serine-threonine kinases, hypothalamic-pituitary-ovarian axis, play behavior, sensor, cell cycle quiescence, molecule, reproductive biology, verification, fluid flow, forkhead box protein o1, forkhead box protein o3

Issue Section: Male and female fertility preservation

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