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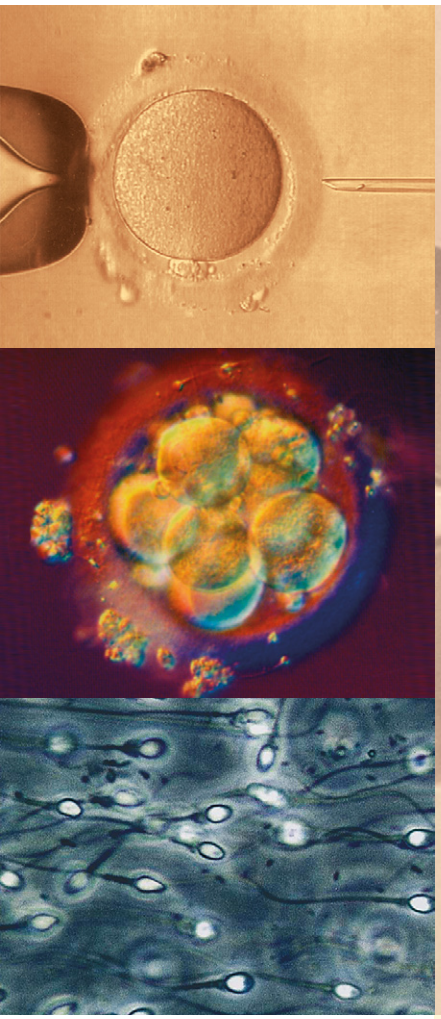

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Omics: Tools for Personalized Reproductive Medicine

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With the development of new technologies for assaying biological activity on a global basis in experimental samples, various new "Omi" approaches involving transcriptomic, proteomic, or metabolomic profiling of oocytes, follicular cells, embryos, or culture media have been applied to predict oocyte competence, embryo quality and pregnancy outcome in assisted reproductive technologies (ART). Currently, embryo selection in IVF or ICSI is mainly based on morphological criteria. However, morphological aspects of embryos are not sufficient to predict a successful implantation and pregnancy. Today, embryo selection based on Omics analysis results an improving IVF success and lead to routine single embryo transfers (SET). **J Reproduktionsmed Endokrinol 2010; 7 (4): 229–32.**

Key words: biomarkers, transcriptomics, proteomics, metabolomics, embryo selection

Introduction

Omics are emergent technologies that can be applied to study large sets of biological molecules. Omics is the large-scale study of genes (genomics), transcripts (transcriptomics), proteins (proteomics), metabolites (metabolomics) and is both the foundation and the driving force for systems in biology [1]. This technologies are enable to identify and quantify all of the components in cellular systems with spatiotemporal resolution, thereby dissect the intracellular pathways can yield mountains of new information in a relatively short time. Such approach offers an opportunity to investigate the relationships between an organism's genotype and its resulting phenotype (Fig. 1). Currently, Omics technologies including DNA sequencing for genomics; DNA microarrays for transcriptomics; mass spectrometry (MS) and protein arrays for proteomics; and for metabolomics, Raman's or near infrared technics are used in some clinical applications area. These emergent technologies are managed by a multidisciplinary team of scientists in a workflow, from sample collection and preparation through analytical operations to processing of raw data and analysis of the processed data. Each step of the pipeline requires meticulous planning in order to extract the optimal amount of reproducible data and translate its biological significance. The advent of access to comprehensive sets of information has brought a new way of global thinking to biological questions, and analysis using these sets is increasingly the choice for many investigations. The aim of this review is to explore the use of Omics in assisted reproductive technology (ART).

Omics and ART

Recently, Omics applications in ART have become feasible. This is due to a spectacular increase in the sensitivity, resolution and throughput of Omics based assays. Although, the number of Omics techniques is expanding, the three most developed Omics technologies and used in ART are transcriptomics, proteomics and metabolomics (Fig. 2). These methods may contribute in the design of a non-invasive approach (i) to assist for embryo selection in single embryo transfers (SET) program, (ii) to evaluate the impact of stimulation protocols on endometrial receptivity and (iii) to identify proteins which predict for normal or degenerative evolution of embryo. Omics new emergent technologies are providing investigators with tools that may help understand the relationships between the oocyte and cumulus cells (CCs) surrounding egg, the dialogue embryo with the endometrium, and the identification new biomarkers to predict the success of early embryo development and embryo implantation.

Transcriptomics Approach

Transcriptomics refers to the comprehensive scanning of the nearly fifty thousand known genes that are transcribed into RNA molecules from the three-billion-letter human genome. The study of transcriptomics examines the expression level of mRNAs in a given cell population, often using high-throughput techniques based on DNA microarray technology. This technology has been successfully applied to the high performance expression of many thousands of genes in a single experiment. Monitoring changes in gene transcription on a genome-wide basis allows identification of groups or clusters of genes that are functionally related to a cell or tissue phenotype. With the development of microarray technology, a number of research groups, have been interested in assessing gene expression in human oocytes [2], cumulus cells [3, 4], early embryo development [5], and endometrium [6–8], aiming to improve understanding of the poorly defined events occurring during oogenesis, embryogenesis and implantation. Analysis of oocyte maturation using microarray techniques could help to identify the genes involved in the processes of meiotic and cytoplasmic oocyte maturation and the specific checkpoints regulating acquisition of full competence for ovulation. Differences in the global mRNA transcript profile have recently been reported between mature oocytes (metaphase II, MII) and immature oocytes (germinal vesicle (GV) and metaphase I (MI)) in mouse and human oocytes [2, 9–12]. Using the Affymetrix Human GeneChip, our group identifies new potential regulators and candidate

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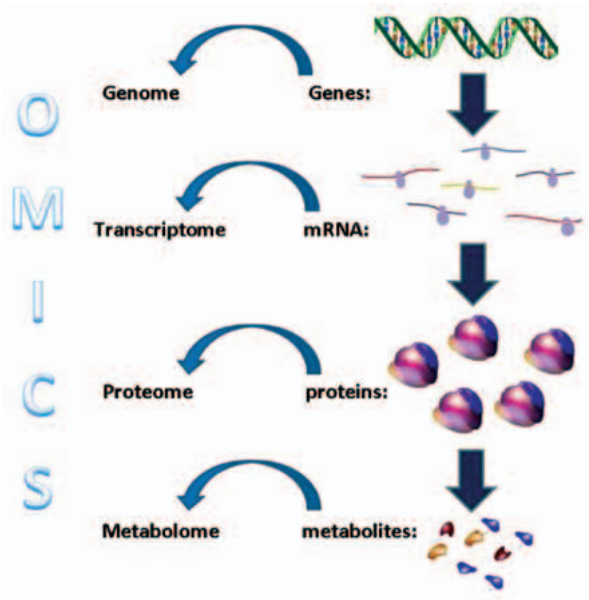

Figure 1: A schematic diagram outlining the complexity of cellular function including associated omics technologies; genomics, transcriptomics, proteomics and metabolomics that contribute to the study and understanding of biological systems.

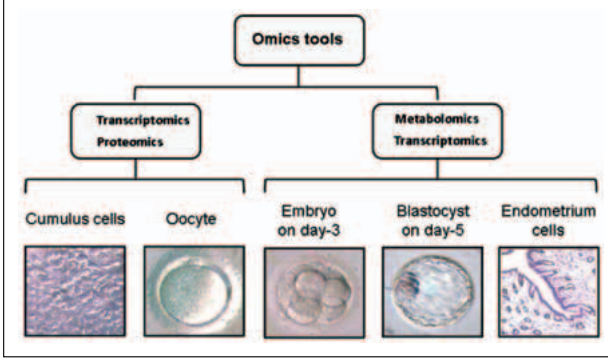

Figure 2: Summary of early embryo development in human. Omics tools for identification biomarkers of embryo quality by assessing oocytes, cumulus cells, embryo, trophoectoderm and Endometrium.

genes which are involved in human oocyte maturation [2, 10]. Interestingly, we reported minor modification of transcript profile between GV and MI oocytes, in comparison to the MII oocytes. Thus major modifications of the transcript profile appear to occur following MI. We show that aurora kinase C (AURKC) is preferentially expressed during oocyte meiosis. Its key role in male meiosis has been confirmed [13] but its role in oogenesis remains to be investigated. Analysis of the transcriptome of aneuploid and normal oocytes, as determined by comparative genomic hybridization (CGH) analysis of the corresponding polar body, has identified several differentially expressed genes with roles in chromosome segregation during meiosis, including genes affecting cell cycle checkpoints, spindle dynamics, and chromosomal movement [14–17]. Transcriptomics represents a valuable approach to biomarker development. Both technical and statistical advances are currently facilitating the application of this approach to ART. This approach has been used experimentally in humans from throphoblastics biopsies performed on blastocysts. It was thus possible to identify genes involved in adherence or cellular communication with a level expression related to implantation [18]. Recently, our team reported for the first time the human trophoectoderm (TE) on day-5 transcriptome by whole genome expression profiling, and we compare this transciptome with that of the embryo on day-3, in order to identify the genes involved in the TE specification and in initiation of pluripotency [unpublished data]. This data establish a solid basis for future studies in early embryo development that will help to identify candidate genes for blastocyst viability. More attractive prospects for in vitro fertilization (IVF) may prove to be transcriptomic analysis of cumulus cell gene expression, as these cells can be tested without compromised the viability of the associated oocyte. Cumulus cells (CCs) share the same follicular environment as the oocyte with which they are associated. Data about biomarker expression in these cells would give more precise information of the microenvironment in which the oocyte matured and will help biologists to achieve a better capability of selecting embryos competent for single transfer. The classical methods to select healthy embryos under IVF and ICSI conditions are based on morphological criteria such as early embryonic cleavage, the number and size of blastomeres, fragmentation degree, and the presence of multi-nucleation at the 4- or 8-cell stages [19]. However, most studies suggest, that embryos with proper morphological appearance alone are not sufficient to predict a successful implantation. Beyond the criteria of embryo selection, defining oocyte quality remains one of the most difficult challenges [20]. Considering the limitation of morphologic evaluation and cytogenetic screening methods, there is now a movement towards more sophisticated, high-performance technologies and the emerging Omics science. An indirect approach for predicting embryo and pregnancy outcomes has been recently reported by using transcriptomic data of CCs gene expression [3]. The CCs are abundant and easily accessible, which makes them an ideal material to use for the potential assessment of oocyte and embryo quality. Data concerning biomarker expression in these cells should yield more precise information, improving the embryologists' capacity to select competent embryos either for fresh replacement or for embryo freezing. Some studies have been reported by studying genes expression profile of CCs or granulosa cells (GCs) using microarrays or reverse transcription-polymerase chain reaction (RT-PCR) and quantitative RT-PCR to identify candidate biomarkers for oocyte quality and competence [21–24], for early embryo development [25–27] or embryo quality and pregnancy outcome [3, 4, 28].

Transcriptomic approaches have emerged to identify biomarkers of the human implantation window, a short period in which endometrium becomes receptive to the embryo. Using microarray technology for analyzing human biopsy samples, several studies have reported modifications in gene expression profiles associated with the transition of the human endometrium from a pre-receptive (early-secretory phase) to a recep-

tive (mid-secretory phase) state during a natural cycle [6, 29, 30]. The comparisons of gene expression profiles of endometrial cells between natural and stimulated cycles showed the presence of the two endometrial profiles and very few genes can be considered as potential biomarkers of endometrial receptivity [7, 8]. Additional studies should be performed in order to test the predictive value for the evaluation of endometrial receptivity during implantation window under stimulated cycle for IVF.

Proteomics Approach

Proteomics describes the changes in all proteins expressed and translated from a single genome [31]. The human proteome, estimated at over a million proteins, is both diverse and dynamic. Using high resolution two-dimensional protein electrophoresis (2D-PAGE) after metabolic labeling with [35S]-Methionine, Hamamah et al. [32] profiled protein expression in cumulus cells (CCs) of MII oocytes obtained after two different hyperstimulation protocols (rFSH versus hMG). The analysis was done on CCs from 2 cIVF cycles on the same patient and then extended on CCs from individual oocytes from 2 groups of patients. In this study, Hamamah et al [32] have shown that CCs from single oocytes have robust levels of protein expression into 600–800 protein spots. Comparison of CC protein expression from oocytes obtained from the same patient but after 2 different hyperstimulation protocols shows that the type of hormonal treatment influences CC protein expression.

The analysis of the protein composition of the embryo involves a different challenge because of the low concentration and wide dynamic range of the population of molecules which need to be analyzed, and because, unlike mRNA, it is not possible to amplify proteins for analysis. Current methodologies for proteomics follow two principal steps. Proteins are separated to provide a sample with decreased complexity and then mass spectrometry (MS) is used for protein identification. Separation techniques include surface-enhanced laser desorption ionizing time of flight (SELDI-TOF), two-dimensional gel electrophoresis (2D-GE) and liquid chromatography (LC). Recent advances in mass spectrometry (MS) have led to the development of methods sensitive enough to allow the secretome examination of single oocytes and embryos. The secretome has been defined as the subset of secreted or consumed proteins that can be found in the environment where the oocyte or embryo grows. Dominguez et al. [33], compared blastocyst conditioned media with control medium using protein microarrays, thus revealing increased expression of the interleukin 10 (IL-10) and soluble tumor necrosis factor (TNF) receptor 1 (TNFR1) and decreased expression of stem cell factor (SCF) and chemokine (C-X-C motif) ligand 13 (CXCL13) [33]. Others studies have provided evidence for a link between the level of cytokines in human follicular fluid (hFF) and the implantation potential of the embryo resulting from the oocyte from this follicle. Using Luminex Technology, Ledee et al. [34] demonstrated that only granulocyte colony-stimulating factor (G-CSF) was particularly elevated in the fluid of follicles corresponding to embryos with high implantation potential and detected significantly higher levels of interleukin 10 (IL-2) and interferon (IFN-gamma) in hFFs whose oocytes generated early cleaving embryos.

Numerous endometrial proteins have been suggested as potential biomarkers of endometrial receptivity based on their sequential temporal expression with respect to the implantation window. Glycodelin A, αVβ3 integrin, osteopontin, LIF, colony stimulating factor 1 (CSF1) protein can be detected in the early-secretory phase with a maximal increase observed between days 19 and 25, coinciding with the implantation window, with none or low levels in the proliferative endometrium [35]. Further studies will help to confirm the advantageous applications of proteomics testing for IVF.

Metabolomics Approach

Metabolomics aims to identify and quantify the global composition of "metabolites" of a biological fluid, tissue, or organism [36]. The "metabolome" (analogous to the transcriptome or proteome) would refer to the comprehensive catalogue of metabolites in a specific organ or compartment under a set of conditions. Recently, this approach is being applied to the study of human embryos [36–39] and oocytes [40]. Because, of the chemical diversity of cellular metabolites, no single analytical platform can measure the metabolome in a cell. However, measuring the metabolome is a considerable analytical challenge. This is due to absence of methods to amplify metabolites (e.g. as may be done with DNA or RNA) – therefore increasing sensitivity – and the labile nature of many metabolites, their chemical heterogeneity and complexity. Many significant technological advances have recently been made in instrumentation related to metabolomics approach. Rapid technological advances in high-performance experiment based on nuclear magnetic resonance and mass spectrometry have enabled us to simultaneously detect a wide range of small molecules. More recently, the development of a screening technology using Raman and near-infrared (NIR) spectroscopy were used to detect biomarkers in spent culture medium with differences in algorithms generated for positive compared to negative in vitro fertilization outcomes [41, 42]. NIR analysis is not typically used for target metabolite identification, but is used for overall spectral profile comparisons. Few studies using single embryo transfer (SET) model on Day 2 and 3 showed higher mean viability scores for embryos that resulted in a pregnancy with fetal heart activity, compared with those that did not [38, 43]. They showed that metabolomic profiling of embryo culture media was independent of morphology. Large-scale, prospective studies are necessary to relate the metabolic profile of medium to the developmental potential of human oocyte and embryo.

Conclusion

The final objectives of Omics in IVF program are: (i) to help select viable embryo(s) and to maximize the chance of pregnancy by screening the endometrial receptivity; (ii) to reduce and eliminate the risks of multiple pregnancies resulting from IVF treatment; (iii) to estimate the overall viability of the cohort of embryos, (iv) to economize the IVF treatment options, (v) to evaluate the embryo health and (vi) to evaluate the impact of controlled ovarian stimulation protocols. However, the interpretation and management of the massive data generated by Omics approaches still re-

quires development of efficient statistical algorithms and bioinformatics tools. The future promises to be bright with the addition of these tools to the IVF centers once the techniques are customized to single cells (oocyte) and embryos, validated, and ultimately introduced to the embryology practice. The challenge now is to correlate gene/protein/metabolite function and regulation to specific events in early embryonic development. A multitude of advantages may ensue from the use of a rapid, non-invasive and reliable technology as an adjunct to embryo assessment for clinical applications. An improved understanding of embryo viability should help to identify the healthy embryos that will most likely result in pregnancy and allow more accurate decisions in selecting the best embryo for the SET program.

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