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The Need to Develop a Single Multi-OMICS Tool for IVF Embryo Selection

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Introduction

In-vitro fertilization (IVF) patients are often made to rely on the judgement of embryologist to select embryo to be returned to the uterus in each treatment cycle. Most often, patients wish to know how the selected embryos are better off than the rest. This is especially true when they are displayed on the screen looking similar to each other. To an untrained eye, they may pass for the same quality but an embryologist use morphological criteria to distinguish the ones that have better quality. Some have argued that the experience of the embryologist is critical at this stage. But many have failed to understand why best of embryos transferred did not implant whereas poor quality embryos by these criteria have produced pregnancies [1,2]. The problem here is neither the skill of the embryologist nor the criteria for the selection but the complexity of the human embryo. The embryo is a very complex entity, with increasing complexity from fertilization to blastocyst [3]. Fertilization is usually evident by a two pronuclei which contain the whole genetic information of an embryo (genome). Soon after fertilization, a one-cell embryo is formed [4]. In order to cleave, it will require mRNAs (transcriptome) and proteins (proteome) from the maternal egg for initial development until the time when it own genome will be ready to carry on with this process [5]. An apparent feature here is the role of genome, proteome and transcriptome. It has been suggested that a healthy embryo will have less damage in it genome, proteome as well as the transcriptome. Because of the minimal damage, it is expected that less energy will be spent by the embryo to correct any defect so the metabolism (metabolome) in such an embryo would be quiescent rather than active [6]. It is therefore needful that the whole component that contributes to the complexity of the human embryo be holistically evaluated. The present morphological assessment criterion does not provide information to evaluate critical pathways of the embryonic genome, proteome, transcriptome and metabolome. These pathways have significant impact on viability of an embryo [7,8]. Recent efforts to address embryonic pathways had been component driven. This has greatly enriched our knowledge about the genetic sequence of an embryo and revealed the role of carrier molecules in altering embryonic genetic information [9-16]. Information about the protein an embryo secretes and metabolic profile of spent media has shown potentials in distinguishing between culture media from implanting and non-implanting embryo [17-21]. Also, embryos have been successfully interrogated to tell when and where gene expression is turned on or off as well as the number of RNAs involved to know how the gene is being expressed [22]. These are landmark achievements that have failed to improve on embryo selection significantly because they are component driven. Multi-OMICS is the greatest innovation the IVF world is anticipating. This is because it could allow information from the different pathways of genomics, proteomics, transcriptomics and metabolomics to be integrated simultaneously from a drop of spent media (Figure 1). The benefit of this approach is that human embryo can be evaluated holistically to allow a gene, protein or metabolite that is poorly expressed in a single 'OMICS system due to low frequency to be captured by another 'OMIC system where it frequency is high. More so, single 'omic system only captures the activity that relates to it. For example, genomic sequencing only captures structural variations, but not RNA level. The RNA level is revealed when another 'OMIC technology such as RNA-seq is applied [23]. This may be one reason why researchers have failed to discover reproducible biomarkers that have the capability of predicting viability in embryo to approach 100% accuracy from a single 'OMIC technology till date.

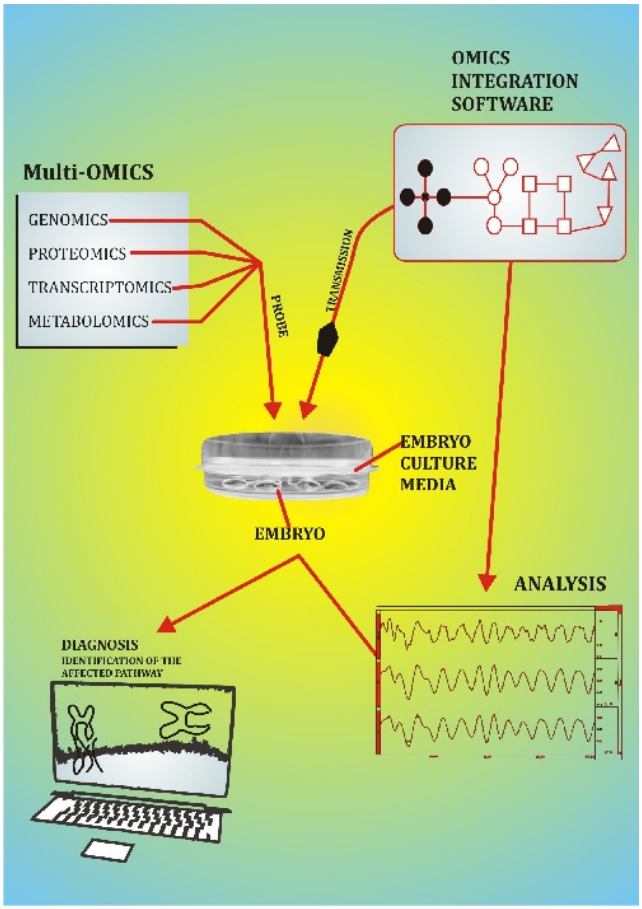

Figure 1: A schematic outline of the steps to integrate multi-OMICS data for identification of any abnormality in an embryo.

Multi-OMIC system should be able to tell if an embryo has normal genes, proteins, ribonucleic acids and metabolic products. Any single embryo that is considered normal by this technology may be capable

of producing a clinical pregnancy. If a single technology is able to assess all these parameters, the possibilities of selecting a single embryo from a cohort that is viable may be increased. This may discourage multiple embryo transfer and reduce multiple births. A technology like this should be simple, rapid and affordable and should only be introduced after it has been properly validated.

One potential bottle neck to developing such a novel technology is proper homogenization of data in experiments and analytical protocols used in developing the individual OMIC biomarkers. This is necessary to avoid false interpretation due to false positive or negative data set as more potential biomarkers of embryo viability are discovered. Another potential bottle neck is developing a computational model that will allow unification of the different data set in a single platform. These bottle necks could be surmounted if skilled professionals in the different disciplines necessary for this discovery are involved early in the research. Only professionals that can apply best practices in sample collection, preparation and analysis should form part of the team. Translational Medicine tools and structures should be properly deployed for effective integration of these disciplines. Developing such a holistic system for selecting embryo will be ideal and better driven by a translational research team that will provide an interdisciplinary and multi-frontier approach.

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