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Symposium: Genetic and epigenetic aspects of assisted reproductive technologies

Introduction: Application of genetic advances to assisted reproduction technologies

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Abstract

Assisted reproductive technologies are common, and successful, therapies to treat infertility. However, challenges in improving the success of assisted reproductive technology, broadening the availability and applicability of the technologies, and minimizing complications and risks continue to confront the field. The science of genetics, including epigenetics and affiliated branches, is undergoing an explosion in the development of new technologies and knowledge. These advances can and will improve and alter the practice of assisted reproductive technology.

Keywords: *embryonic stem cells, infertility, new technologies, nuclear reprogramming, predictive, therapy*

Introduction

Assisted reproductive therapies are common, and successful, methods of treating many types of infertility. In fact, in-vitro fertilization (IVF) is responsible for approximately 1 of every 50 births in Sweden, 1 of 60 births in Australia, and 1 of 80–100 births in the United States (Van Voorhis, 2007). Nevertheless, significant challenges, such as multiple pregnancy, unexpected poor hormone response, fertilization failure, poor embryo development, and adverse outcome in offspring continue to

challenge the field. The resolution of these challenges will largely depend on the application of knowledge and technology gained from the basic sciences, including the exciting advances currently being made in the field of genetics.

Scientific advances in the area of infertility are of limited benefit if they do not change personal preferences, enlighten decision-making options, or improve medical options available to the patient. In that regard, the potential benefits of genetic advances in medicine have not been undersold; in fact there has been a long-standing prediction and hope that the application of advances in genetic knowledge will revolutionize medical therapy. Elias Zerhouni, director of the National Institutes of Health in the USA, has proposed that such advancements will transform medicine into an era in which medicine is more predictive, personalized, pre-emptive, and participatory (Zerhouni, 2007). Assisted reproduction therapy should be improved in each of these areas, known as the 'four Ps', by the application of genetic advances and knowledge to clinical therapies. Additionally, a logical fifth 'P' may be added to the list, the development of new 'pathways' to exciting and beneficial new therapies.

In this Guest Symposium in *Reproductive BioMedicine Online*, a sampling of topics addressing issues involved in assisted reproduction therapy that may be improved by genetic advances is presented by leading researchers in the field. While not all applicable topics are addressed, the authors cover a wide range of topics that address the potential of genetic advances to improve assisted reproduction therapy by improving the predictive ability of the pre-IVF evaluation, using those data to personalize therapy, pre-emptively making adjustments to improve outcome quality, and increasing the participatory nature of the process. Lastly, new technologies provide a glimpse into the pathways towards the future of assisted reproduction therapy.

Can we improve our predictive ability prior to assisted reproduction treatment?

IVF is a costly and invasive procedure for which informed decision-making is lacking in regards to the utility of the therapy in providing a pregnancy, therapeutic options to maximize success, and options to avoid multiple pregnancies, ovarian hyperstimulation, or other negative outcomes. While some useful assays are available to evaluate the prospect of successful ovarian stimulation and fertilization potential, assisted reproduction treatment itself is essentially the first, and only, bioassay to predict assisted reproduction therapy outcome. While indicators such as age and prior fertility are of some value, essentially no assays are available to predict embryo quality or uterine receptivity.

Some of the options for improving the predictive ability of the pre-assisted reproduction technology work-up are addressed in the articles presented in this Symposium. For example, the development of effective assay to predict gamete function prior to IVF therapy could help to avoid unnecessary financial and emotional burdens, and help to avoid potential medical complications. In that regard, Carrell presents an overview of current and future areas in which prospective sperm testing may be of benefit in predicting embryo quality, such as genome dosage, genome integrity, and genome packaging issues. Additionally, Chatzimeletiou and co-authors address the issue of the function of the paternally derived centrosome, and the role of defective centrosome function in chaotic embryogenesis. Rousseaux and co-authors address chromatin changes in the gametes and embryo itself, an area of study with profound implications for the successful birth of healthy offspring.

Another area of research is the identification of gene variations involved in male and female infertility, and the role that specific variants may have on gametogenesis and embryogenesis. Some gene variants involved in infertility have been identified, and Nuti and Krausz provide an update on variants involved in male infertility. Chantot-Bastaraud and co-authors complement this discussion by providing an update on chromosome defects in men undergoing assisted reproduction technology. Martin expands the discussion with an analysis of the effects of abnormal recombination on sperm aneuploidy.

Can we improve assisted reproduction therapy quality by personalization?

Improving diagnostic options to better predict IVF outcome has profound ramifications for personalizing assisted reproduction therapy to obtain a better outcome. For example, the understanding of sperm centrosome or chromatin defects should not only be useful in predicting potentially poor outcomes, but also ultimately in identifying methods to select non-affected spermatozoa for ICSI or other therapeutic options.

Recent studies on the FSH and oestrogen receptor variants illustrate the effects of individual variability on outcome and the potential for customizing therapy based on the patient's genome (de Castro *et al*., 2005; Altmae *et al*., 2007). Similarly, it is possible that genetic variations in patients will predispose them to varying outcomes after embryo culture with different media. Genetic variability may lead to customized, or personalized, therapy essentially in all stages of assisted reproduction.

Can pre-emptive actions preserve fertility, improve therapy, and reduce risks?

The identification of gene and chromosome variants predictive of poor embryogenesis or fetal development will undoubtedly reduce risk to the offspring, along with reducing emotional and financial toll of such events. Additionally, it is extremely likely that preimplantation genetic screening and diagnosis (PGS and PGD) will continue to develop in scope and accuracy and contribute to improved success rates and reduced risks involved in assisted reproduction. Kuliev and Verlinsky discuss the future of PGD and PGS in a provocative article contained in this Symposium.

Gene polymorphisms should be considered as risk factors rather than direct aetiological causes of disturbances of

spermatogenesis. It is likely that some polymorphisms, only in association with a specific genetic background or with environmental factors, lead to testicular dysfunction. The role of genetic background seems to be especially relevant for one of the most promising genetic risk factors, the gr-gr deletions, as described by Nuti and Krausz. Studies have also shown that environmental factors appear relevant for polymorphisms of the oestrogen and androgen receptor genes, and of genes involved in oxidative stress. However, studies focusing directly on gene–environmental interaction are completely lacking in this field. In the future, those studies will allow an even greater pre-emptive effort to avoid and correct infertility.

Will the participatory role of the patient be different?

Assisted reproduction therapy is unique compared with many areas of medicine in the USA and some other areas due to the self-pay nature of the field. Therefore, patients are often very involved in researching options and clinics. Genetic advances may further improve this process by highlighting the unique nature of each patient. It is possible that understanding individual variation will focus assisted reproduction technology clinics even more on the patient, and patients will be more involved in selecting options personalized to their needs.

What are the pathways to future therapies?

Each article contained in this special Symposium points to potential future technologies and changes in the practice of assisted reproduction therapy, but some address the issues very directly. For example, Nagy and co-authors describe the status and potential of developing artificial gametes for patients with no current options for treatment with their own gametes. Additionally, the area of stem cells, somatic cell nuclear transfer, and cloning are addressed by a very distinguished and forward-looking group of scientists in exciting papers by Wakayama *et al*. and Van Blerkom.

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