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Review

Modeling the interaction of gametes and embryos with the maternal genital tract: From in vivo to in silico

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Abstract

Understanding the complex interaction between gametes or embryos and the maternal genital tract requires the use of experimental models. The selection of the right model is an important task to undertake, and despite many new developments in this area, an ideal model system has not yet been developed. In this review article, we focus on how the most appropriate model species and model system can be selected, each with its particular advantages and disadvantages. Selection criteria need to be based on the evaluation of the aim of the experiment, the tools that are available to the scientist, and the ethics that are involved in working with particular animal species and model systems. Society and politics direct scientists to ‘‘Refine, Reduce, and Replace’’ the use of experimental animals, which means that the use of in vivo models is increasingly being discouraged. An in vivo model allows experimentation in the full biological environment of a living organism. In contrast with in vivo models, in vitro models are less complex and are abstracts of in vivo systems, leading often to results that are different from the in vivo situation. If an investigator could understand all the components of a complex biological system and re-create them as individual smaller models in a computer, he or she could create in silico models that would completely represent the complexity of in vivo models. We predict that in the future, in silico modeling will be the natural departure from in vivo, in situ, and in vitro modeling approaches. In addition to numerous advantages that this modeling approach can bring to studying maternal interaction with gametes and embryo, it is perhaps the only true alternative method to animal experimentation.

Keywords: Animal replacement; In silico; In vitro; In vivo; Model systems

Contents

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1. Introduction

In mammals, the maternal reproductive tract serves multiple purposes, such as selecting the fittest sperm for fertilization, allowing undisturbed early development of the embryo, taking part in placenta formation, and nurturing the fetus during pregnancy [1,2]. Understanding the details of interaction between the embryo and the maternal reproductive tract is of major importance, as this communication not only results in pregnancy but also seems to influence the future health of offspring [3]. This is an important issue in assisted reproduction used for the treatment of infertility in humans and also in livestock breeding. The first reports on calves and lambs suffering from the large offspring syndrome served as eye openers for the consequences of adverse environmental factors during a vulnerable period of life [4–6]. Human epidemiologic studies have likewise demonstrated associations between early life factors and a range of diseases in adulthood. This has led to the development of the Barker hypothesis or the theory of the "developmental origins of health and disease" (DOHaD) [7].

In addition to embryo-maternal interactions, spermatozoa and oocytes communicate with the maternal genital tract, too. The intimate and specific cell-to-cell contacts between spermatozoa or oocytes and female reproductive tract epithelia are not series of coincidences: the tight and specific binding of spermatozoa to oviduct epithelial cells upon arrival in the isthmus serves to suppress sperm motility to assist the conservation of the limited energy reserves in male gametes [8]. Such bound spermatozoa are also uncapacitated and will only be released when they have completed the process of capacitation, during or after ovulation [8]. Sulfated glycoconjugates and disulfide reductants have been identified as powerful inducers of the release of spermatozoa from cultured oviductal epithelium [9]. The counterparts of these molecules in vivo are probably heparin-like glycosaminoglycans and reduced glutathione, respectively, both of which are present in bovine oviductal fluid at increased concentrations during estrus [10,11]. The elucidation of the identity and the function of similar signaling molecules may lead to important applications in the field of infertility treatment and contraception. Whereas in some Western countries more than 3% of babies are born as a result of assisted reproduction [12], contraception remains a major issue worldwide and represents a solution for the rapidly growing human world population, which at present exceeds 6.7 billion. Other potential applications of basic research on maternal communication with gametes and embryos are the development of new sperm diluents, reduction of embryonic losses, and prevention of adulthood diseases with so-called in utero origins, as was recently reviewed [13,14]. The importance of experimental models in this type of research is self-evident [15]. In this review, we will first focus on why we need model systems to learn more about human and animal reproduction. Most importantly, scientists need to select a model species with the aim of the experiment and the available tools in mind. Next we will discuss ethical issues that urge researchers to replace in vivo models, whenever possible, by in situ, in vitro, or even in silico models, with the concomitant advantages and disadvantages.

2. Criteria to take into consideration before selecting a model

Model systems can either be chosen because they represent the species of interest, when a particular characteristic related to this species needs to be investigated, or they can be chosen irrespective of the species, when a general reproductive phenomenon is being investigated. The more a scientist wants to mimic one particular in vivo system, the more he or she will be inclined to select an in vivo model representing the species of interest. We can illustrate this statement by taking the honey bee as an example. The honey bee queen (*Apis mellifera*) mates with several drones during her maiden flight. She will thereafter never mate again but will store the sperm in the spermathecal glands and will selectively release sperm to fertilize her eggs during the next 2 to 7 yr of her life [16]. As such, the honey bee represents an interesting model species for scientists who want to study the exact circumstances that allow for the stored sperm to remain viable for a period of many years. If the molecules involved in this process could be identified, this knowledge can be applied for the