EDITORIAL

The zona pellucida as a gripping object of investigation

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The zona pellucida (ZP) is a layer of extracellular matrix that, in mammals, exclusively surrounds oocytes. To allow fertilization sperm have to penetrate the ZP. When fertilization occurs and the zygote develops into an embryo, the embryo has to hatch out of the ZP at blastocyst stage to allow implantation in the uterus and further on fetal development. Thus, the ZP serves checkpoint functions during reproduction. Beside its role as controlling sperm entry and blastocyst implantation, the ZP is discussed to prevent poly spermy. In addition, the ZP is known to protect the developing embryo from environmental factors. If one of these ZP functions fails, fertility is impaired or even completely blocked. For me the functional complexity of the ZP always was fascinating to study.

If a sexually active, non-contracepting couple is unable to achieve pregnancy within one year, they are defined as infertile. Thousands of clinics all over the world try to fulfill the wish to have children each and every day. Unfortunately, in a lot of cases this is so far impossible, due to various causes. In up to 50% of all cases, the reasons for infertility are still unknown and claimed as being idiopathic. Assisted reproductive techniques (ART) are used to overcome infertility. If the sperm show low quality or if *in vitro* fertilization (IVF) already failed once, the ZP is bypassed by using intra cytoplasmic sperm injection (ICSI). In certain cases assisted hatching is applied in addition to facilitate embryo hatching and thus to increase the implantation rate. Beside the well-known side effects of ART, like health risks to egg donors by hormonal hyper stimulation, bypassing the ZP during ART gives additional risks. 1. By injecting sperm (ICSI), eggs could be fertilized by poor quality sperm, which probably would have never penetrated naturally. 2. By applying assisted hatching, the ZP as a quality checkpoint is bypassed again, which increases embryo implantation but perhaps also miscarriage rates. 3. Overcoming infertility by evading the ZP for sure can help the individual to achieve pregnancy, but so far we do not know in which cases infertility is handed on to the next generation and what will be the long-term outcomes of ART in general. If infertility is inherited, the cases of reproductive failure will increase in the entire population within the next decades, a tendency that is already visible due to other reasons. Thus my personal goal is to shed more light on the complexity of reproduction and keep on studying infertility.

Due to ethical reasons, it is quite often tough to study human systems. Thus, the mouse serves as a model organism by which researchers discovered several genes that are involved in reproduction regarding the ZP and its functions. For example, removing one of the three ZP proteins in mice leads to structural disruption of the ZP (1–3). Depending on the ZP protein that was removed or mutated this can lead to impaired oocyte development, blocked fertilization or decreased embryo development and thus as a further consequence to subfertility or infertility. However, there is only very little known about ZP protein mutations causing infertility in humans (4–7).

An example for a ZP-associated protein that is important for fertility is ovastacin, a protease released by oocytes after fertilization that modifies the ZP (8). Embryos lacking fertilization-triggered ZP modifications are less protected until implantation and thus these embryos are more often lost at a very early stage (9). Ovastacin is also conserved in humans, but so far there are no data available on human ovastacin mutations.

Another example for a protein known to be involved in modulating the ZP is fetuin-B, which was mainly studied by my former colleagues and me. Fetuin-B is a liver-derived protein surrounding oocytes during development to keep the ZP penetrable (10). Fetuin-B deficient (Fetub -/-) mice are infertile due to blocked fertilization. In humans, low fetuin-B serum concentrations were shown to be associated with a low IVF rate (11). These data suggest a similar role of fetuin-B in both species, mice and humans.

Although some of these findings were already discovered more than 30 years ago, translation to human reproduction is rare. This is due to a lot of very different reasons. But even if human material and data would be available one has to keep in mind that the number of cases that show modifications at ZP-associated mechanisms probably are very rare, because before IVF was developed (in the 1950th) these people would not have been able to reproduce. Thus, a huge number of samples have to be analyzed to find single individuals carrying mutations that lead to infertility. Nevertheless, due to the use of ART the amount of inherited infertility is likely to increase in the overall population and hence research on reproductive defects should be of common economic interest.

From my point of view, the advantages of combining clinical human and basic research are quite obvious. On the one hand by including human data, one could get a much better understanding of reproduction in mammals which may be also applicable to non-mammals. On the other hand, one could develop more individual treatments for patients, first discovering the cause of the infertility, second treating the infertility more personalized. These are some of the most important goals I would like to get closer within my research career.

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