Preface: Posttranslational Modifications—When the Sperm Cell Meets the Egg

By various accounts, the human genome includes up to 25,000 genes transcribed into messages from which a staggering one million of proteins and protein variants are derived that constitute the human body proteome. While some of this increase between gene and protein is due to alternative transcription and posttranscriptional processing of mRNA by alternative splicing, most of the alternative gene products at the protein level are due to posttranslational modifications (PTM) of nascent proteins. Within the focus area of the present book, reproductive biology, the genomic era armed us with knowledge about transcripts that appear at distinct stages of reproductive process. However, the abundance of a transcript does not directly translate into an abundance of a protein and that in turn is not a direct indicator of biological activity, which is regulated by PTM. The goal of the present book is to increase the awareness of a great variety of PTM observed in gonads, gametes, embryos, and in the male and female reproductive system in general. While far from all-encompassing, some of the most intriguing reproductive strategies, mechanisms, and pathways involving PTM are discussed, with an added angle of evolutionary conservation and diversity.

Posttranslational protein modifications by ubiquitin and ubiquitin-like proteins (e.g., SUMO, NEDD4, NEDD8, and ISG15) involve stable, covalent ligation of one or more molecules of a small chaperone protein that predestines the substrate for proteolytic degradation or alters its function. Protein ubiquitination is important for all phases of spermatogenesis, including germ cell renewal and proliferation, meiosis and post-meiotic differentiation into spermatozoa, reviewed by *Rohini Bose, Gurpreet Manku, Martine Culty, and Simon S. Wing.*

Adding a comparative/evolutionary aspect, *Long Miao and Steven W. L'Hernault* discuss the roles that protein phosphorylation, proteolysis, ubiquitination, and palmitoylation play in the spermatogenesis and sperm function of nematode worms *Caenorhabditis elegans* and *Ascaris suum.* Spermatozoa of both of these species use a unique form of amoeboid motility termed crawling, and many posttranslational-modification-controlled aspects of nematode spermatogenesis and motility are different from mammals.

Even though they are morphologically fully differentiated, the testicular spermatozoa in mammals are not yet competent to fertilize an oocyte. For this to happen, mammalian spermatozoa have to travel through epididymis where they undergo a complex change referred to as epididymal sperm maturation. This involves posttranslational modifications of structural sperm proteins, as well as modification of sperm surface by addition or removal of sperm surface proteins via apocrine protein secretion and targeted proteolytic processing. While this complex transformation into a fertilization competent spermatozoon is not yet fully understood, some of the recent work on epididymal function has been focused on PTM of sperm and epididymal luminal fluid proteins, reviewed by *Gail A. Cornwall.*

Mammalian vitelline coat, the zona pellucida (ZP) is a unique, specialized extracellular matrix composed of three or four heavily glycosylated proteins, some of which have the ability to bind spermatozoa and induce sperm-acrosomal exocytosis. Zona protein glycosylation and proteolysis determine sperm–oocyte interactions and anti-polyspermy defense. While often reviewed from the point of view of murine model or human ZP data, the wealth of data from ungulate models is seldom a subject of a comprehensive review. This gap is now filled by *Naoto Yonezawa*, discussing protein glycosylation and other posttranslational modifications of porcine, bovine, murine, and human ZP proteins.

While traditionally thought to be primarily confined to cell cytoplasm and nucleus, the ubiquitin-proteasome system (UPS) has been revealed in a surprising extracellular context in several systems. Among them, the functioning of ubiquitin-conjugating machinery and that of the sperm borne 26S proteasome, the endpoint protease of UPS, plays a surprisingly well conserved role in sperm penetration through the oocyte vitelline coat. While relevant to mammals including humans, some of the earliest studies of gametic extracellular UPS were conducted in ascidian and echinoderm animal models, and are reviewed in the chapter by *Hitoshi Sawada, Masako Mino, and Mari Akasaka.*

The intracellular balance of polymeric and free, unconjugated ubiquitin is maintained by deubiquitinating enzymes, which also have the ability to reverse protein ubiquitination. Among them, the ubiquitin C-terminal hydrolase (UCH) family enzymes are some of the most abundant proteins found in mammalian oocytes and embryos. *Namdori R. Mtango, Peter Sutovsky, and Keith E. Latham* discuss the recent evidence for the involvement of UCHs in the regulation of oocyte cortex and meiotic spindle during oocyte maturation, fertilization, and preimplantation embryo development.

Besides studying embryo development after natural or assisted (*in vitro*) fertilization, somatic cell nuclear transfer (SCNT) offers an intriguing alternative model for understanding early development. Donor cell nuclear remodeling is a central event during embryo reconstruction by SCNT, which is, together with the subsequent reprogramming of donor cell genome, tightly regulated by PTM of the DNA-packaging histone proteins, such as acetylation and ubiquitination. Additionally, establishment of the first mitotic spindle differs with regard to protein content, localization, and PTM between IVF and SCNT zygotes. These and other aspects of PTM influence on embryo development after SCNT are reviewed by *Keith E. Latham.*

Protein phosphorylation is paramount to cellular signaling in every system, including the reproductive one. Strategies for success of species led to evolution of unique protein kinases within the phylogenetic tree. Chapter 3 by *William H. Kinsey* provides an evolutionary insight into the role of protein kinases, and tyrosine kinases in particular, in the regulation of cellular signaling during oocyte maturation and fertilization in animal models ranging from insects to mammals.

Cytoskeleton provides the structural scaffold for meiosis, fertilization, and early embryo polarization and differentiation during preimplantation development. Furthermore, cytoskeletal tracks and cytoskeleton organizing centers are indispensable for cellular signaling and cargo trafficking in germ cells, gametes, and embryos. *Heide Schatten and Qing-Yuan Sun* discuss how the phosphorylation of cytoskeletal and cytoskeleton-associated proteins and structural modifications of cytoskeletal proteins such as the acetylation, glycosylation, ubiquitination, tyrosination, polyglutamylation, poly-glycylation, sumoylation, and palmitoylation regulate microtubules, microfilaments, and intermediate filaments in gametes and embryos.

Following fertilization and pre-embryo development, the success of mammalian pregnancy depends on the remodeling of the uterine lining, the endometrium, and the modifications of intrauterine environment that favor embryo implantation and development to term. Chapter 2 by *Thomas R. Hansen and James K. Pru* summarizes the contribution of PTM to these crucial steps of mammalian reproductive process, with particular focus on protein ISGylation, a ubiquitination-like protein modification that is significantly upregulated as a part of maternal response to the developing conceptus.

As is the case in all areas of biology and medicine, the knowledge of posttranslational protein modifications and their outcomes will continue gathering interest of reproductive biologists and clinical practitioners of assisted reproduction. In addition to better understanding of life, this learning process will lead to new or optimized assisted reproductive therapies for infertile couples, to improvement of reproductive health of our population, to the optimized strategies for stem cell derivation and animal transgenesis, and for increased reproductive performance of livestock animals.

Columbia, Missouri Peter Sutovsky

http://www.springer.com/978-1-4939-0816-5

Posttranslational Protein Modifications in the
Reproductive System
Sutovsky, P. (Ed.)
2014, XIV, 249 p. 40 illus., 29 illus. in color., Hardcover
ISBN: 978-1-4939-0816-5