Contents

Preface, vii

Germline Stem Cells, 1
Allan Spradling, Margaret T. Fuller, Robert E. Braun, and Shosei Yoshida

Molecular Regulation of the Mitosis/Meiosis Decision in Multicellular Organisms, 21
Judith Kimble

Function of the Sex Chromosomes in Mammalian Fertility, 37
Edith Heard and James Turner

Unique Aspects of Transcription Regulation in Male Germ Cells, 55
Helen White-Cooper and Irwin Davidson

Translational Control in Oocyte Development, 71
Joel D. Richter and Paul Lasko

RNA Granules in Germ Cells, 85
Ekaterina Voronina, Geraldine Seydoux, Paolo Sassone-Corsi, and Ippei Nagamori

Germ Cell Intercellular Bridges, 113
Michael P. Greenbaum, Tokuko Iwamori, Gregory M. Buchold, and Martin M. Matzuk

Small Noncoding RNAs in the Germline, 131
Jonathan P. Saxe and Haifan Lin

Developmental Control of Oocyte Maturation and Egg Activation in Metazoan Models, 147
Jessica R. Von Stetina and Terry L. Orr-Weaver

Mammalian Genomic Imprinting, 167
Marisa S. Bartolomei and Anne C. Ferguson-Smith

Nuclear Transfer to Eggs and Oocytes, 185
J.B. Gurdon and Ian Wilmut

Selection in the Rapid Evolution of Gamete Recognition Proteins in Marine Invertebrates, 199
Victor D. Vacquier and Willie J. Swanson

Index, 217
Preface

The famous quotation by Charles Darwin, “It is not the strongest of the species that survives, nor the most intelligent, but the one most responsive to change,” beautifully illustrates the unique role of germ cells in the maintenance and evolution of the species. To be inherited, the changes to which Darwin refers need to occur in germ cells. For this, and many other reasons nicely developed in this book, germ cells have long fascinated a large number of researchers over many decades. Restricted for many years within the boundaries of descriptive science, the field of germ cell research has dramatically benefited from the development of molecular biology techniques, of genome-wide array approaches, and of cell- and tissue-specific gene ablation by homologous recombination, as well as from the increasing number of species in which experiments can be done. The past two decades have witnessed the accumulation of a spectacular amount of knowledge, including several discoveries that have fundamentally altered the manner in which we look at how germ cells develop and function.

The idea for this book originated from a desire to incorporate in a single volume not only the remarkable advances that have been made in the field but also the emerging concepts and hypotheses that currently drive thinking and experimentation in this field. In most cases, the authors have aimed to describe both facts and concepts arising from studies across multiple species. This approach reveals common themes, as well as intriguing examples of diversity. We, the editors, have worked with the authors to ensure that overarching ideas are linked among the chapters.

Germ cell development is unique in the way it generates the haploid cells responsible for perpetuating the species. The resulting germ cells are virtually totipotent; they will generate all possible cell types and tissues after fertilization. How is such a complex and elaborate differentiation program achieved? In what way is it unique with respect to the numerous programs of somatic cell differentiation? These questions have recently acquired even broader interest because of the excitement generated by stem cell biology and the therapies it promises. The intrinsic potential of germ cells to generate a whole new organism relies on very specific and fascinating molecular and cellular pathways operating during their development. Of course, the process of meiosis is one outstanding feature of germ cells that involves a series of highly specialized biochemical and metabolic processes. In addition, germ cell development requires choices between alternative pathways of gene expression, each generating a drastically different outcome. As an example, during mammalian spermatogenesis, spermatogonial stem cells face the choice of self-renewal or differentiation. Whichever pathway they choose, the task is formidable. On one hand, self-renewal is one of the most impressive examples of highly controlled and efficient cell proliferation, one that continues until old age in human males. On the other hand, cells unique in their structure are generated through the differentiation pathway requiring drastic biochemical reorganization and meiotic division. When things go wrong, the outcome can be dramatic, possibly leading to infertility on one hand or cancer on the other.

Two fundamental characteristics underlie the fascination of current germ cell research. First, germ cells must carry out all the basic functions of cells, ranging from transcription to division, but under the control of the germline developmental program, they do so in unusual and exceptionally interesting ways. Second, although the appearance of the exquisitely specialized cells that are gametes differs profoundly among species, in part to allow exploitation of different niches, strikingly
unifying themes arise from the comparison of germ cell development across species. We strove to highlight both of these fundamental features in the organization of this book.

We hope this book will not only serve the aficionados in the field but also be accessible to students and researchers from other fields who wish to discover the fascinating world of germ cells. Indeed, part of our ambition is to motivate new generations of investigators to enter the field. The authors have contributed magnificently toward these goals, and we thank them for their participation.

Finally, we wish to thank the outstanding staff at the Cold Spring Harbor Laboratory Press and their compositors, particularly Hannah Turner at Techset, for their efforts in making this book a reality. Our deep appreciation goes to Project Manager, Barbara Acosta, for her sense of organization, limitless patience, and constant kindness. We also thank Acquisitions Editor, Alex Gann, whose vision and intelligence initiated the process that lead to this work.

PAOLO SASSONE-CORSI
MARGARET T. FULLER
ROBERT BRAUN
Index

A
Acrosome reaction (AR), 205–206
ACT, spermatogenesis role, 61–63
Ago3, 98
Airn, 174
AKAP4, 120
AKT, 14
ALG-2, 127
ALIX, 124–127
AMEIOTIC1, 30
Angelman syndrome (AS), 170–171, 173
APC/G/C, 154, 159
Argonaute, 98–100, 132
Arp2/3, 117
AS, See Angelman syndrome
ATM, 45
ATR, 45
Aubergine, 98, 100
Aurora B, 123
AZF, deletions, 39, 41

B
Balbiani body, 86
BAM, 4–6, 26–27
Beckwith–Wiedemann syndrome (BWS), 170–171
BGCN, 6, 26
Bindin, oyster sperm
structure, 210–211
variability, 211
Bindin, sea urchin
alleles and selection in maintenance, 203–204
EBR1 receptor, 202–204
positive selection in allopatric species, 205
rapid evolution in sympatric species, 203
slow evolution in allopatric species, 204–205
starfish bindin comparison, 201–202
structure, 201
BLIMP1, 13
BWS, See Beckwith–Wiedemann syndrome

C
CAF1, 57
Calmodulin-dependent protein kinase II (CaMKII), 154, 159
CaMKII, See Calmodulin-dependent protein kinase II
CAR1, 101
caudal, translational regulation in oogenesis, 76
Cdk1, 151, 153–154, 156–159, 161
Cdk2, 157
CEP55, 124–127
Chromatid body, 92
COX, See Cyclooxygenase
CPE, See Cytoplasmic poladenylation element
CPEB, 77–79
CPSE, 77–78
CREM, spermatogenesis role, 59, 61–63
CSF, See Cytostatic factor
CSR-1, 100
CTCF, 174, 179
Cup, 72–73
Cyclin B, 153–154, 156–159, 161
Cyclooxygenase (COX), 158
Cyst stem cell, germ line stem cell association, 9–11
Cytokinesis, intercellular bridges, 122–124
Cytoplasmic poladenylation element (CPE), 77
Cytostatic factor (CSF), 153–154

D
DALL Y, 6
DAZ, mouse sex determination, 29
DHH1, 101–102
Dki, 170, 172, 174, 179
DNA methyltransferases, 173, 175–177
Double Y syndrome, 38–39, 48
DREAM, 57–58
DRH-3, 100
DRM, 57

E
EBR1, 202–204
EGG proteins, 156
EGO-1, 100, 102
EKL-1, 100
α-Endosulfine, 157–158
ESCORT-1, 124

F
FBF-1, 25–26
FBF-2, 25–26
Index

Fertilization, See Gamete recognition; Oogenesis; Spermatogenesis
4EHP, 76
Fusome, ring canal, 116

G
Gamete recognition
bindins
  oyster sperm
    structure, 210–211
    variability, 211
  sea urchin
    alleles and selection in maintenance, 203–204
    EBR1 receptor, 202–204
    positive selection in allopatric species, 205
    rapid evolution in sympatric species, 203
    slow evolution in allopatric species, 204–205
    starfish bindin comparison, 201–202
    structure, 201
lysin, abalone sperm
  crystal structure, 207
  gene duplication in evolution, 207–208
  positive selection, 206
  vitelline envelope receptor for lysin, 208–209
marine invertebrate models, 200
mussels, 207
overview, 199–200
prospects for study, 211–212
protein module conservation in eukaryotes, 211
selection modes driving rapid evolution of fertilization proteins
  balance between sperm competition and egg polyspermy avoidance, 201
  reinforcement, 200s
  sexual selection, 201
  specialization following gene duplication, 200–201
sperm receptor for egg jelly protein evolution, 205–206
turban snails, 206–207
GASZ, 99
GDNF, See Glial cell-derived neurotrophic factor
Genomic imprinting
diseases, 171
  evolution, 178–179
  functions, 170–172
  gene identification, 169–170
  germline establishment, 175–177
  history of study in mammals, 167–169
  maintenance of imprints, 177–178
  mechanism, 172–175
  prospects for study, 179
Germ granules, See RNA granules, germ cells
Germinal vesicle breakdown (GVBD), 153
Germline stem cell (GSC)
  lineages, 2–3
  mitosis/meiosis transition in Caenorhabditis elegans, 23–26
  niche
    Drosophila
      ovary, 4–6
      testes, 8–12
      maintenance, 2, 4
      mammalian testes, 12–16
    overview, 1–2
  phylogenetic distribution of female cells, 6–8
GLD-1, 25–26
GLD-2, 25–26
GLD-3, 25–26
Glial cell-derived neurotrophic factor (GDNF), 14–15
GLP-1, 25
GPPX3Y motif, 126
grk, translational regulation in oogenesis, 75–76
GSC, See Germline stem cell
GVBD, See Germinal vesicle breakdown

H
H2AX, 45
H19, 169, 173–175, 178–179
Hen1, 99
Hrp48, 84
hunchback, translational regulation in oogenesis, 76

I
ICR, See Imprinting control region
Igf2, 169–170, 173–175, 177–179
Igf2r, 169, 174–175, 178
IMC, See Intermitochondrial cement
IME1, 23
Imprinting, See Genomic imprinting
Imprinting control region (ICR), 170, 173–177
Intercellular bridges, germ cells
  mammals
    cytokinesis, 122–124
    formation, 124–126
    functions, 126–127
    overview, 118–122
    overview, 113, 115
    prospects for study, 127
  ring canals in Drosophila, 114–117
Intermitochondrial cement (IMC), mouse spermatocytes, 95–96
Inx2, 157

J
JAK-STAT signaling, germline stem cells, 4–5, 10–11
K
Kelch, 117–118
KIF17b, spermatogenesis role, 61–63
KIF4, 123
Klinefelter syndrome, 38–39

L
L3MBTL, 178
LH, See Luteinizing hormone
LIN-3, 25
LIN28, 14
LINC, 57–58
Luteinizing hormone (LH), oogenesis regulation, 153
Lysin, abalone sperm
crystal structure, 207
gene duplication in evolution, 207–208
positive selection, 206
vitalize envelope receptor for lysin, 208–209

M
MAEL, 99
Mael, 141
Major sperm protein (MSP), 155, 160–161
Male sex chromosome inactivation, See Y chromosome, 44
Matrimony, 158
MBK-2, 156, 161
MEI-1, 156
Mei2, 23
Meiosis, See also Mitosis/meiosis transition
arrest in gametogenesis, See Oogenesis;
Spermatogenesis
general features, 21–22
sex chromosome inactivation, 44–47
Messenger RNA (mRNA), RNA granule regulation
localization, 100–101
stability, 102
translation, 101–102
MEX-2, 156
MEX-6, 156
MgcRac-GAP, 123–124
MicroRNA, See miRNA
Mip120, 57
Mip130, 57
miRNA
characterization and function, 133–134
germline functions, 134
overview, 131
MitoPLD, 96, 99
Mitosis, See also Mitosis/meiosis transition
chromosomal protein exchange in somatic cell
nuclear transfer, 193–194
general features, 21–22
RNA granule function, 100

Mitosis/meiosis transition
emerging themes, 30–31
general features, 21–22
molecular regulation
Caenorhabditis elegans germline stem cells, 23–26
Drosophila cyst formation, 26–27
mouse sex determination, 27–29
plant germline/soma decision, 29–30
yeast overview, 22–23
Saccharomyces cerevisiae, 23
Schizosaccharomyces pombe, 23
prospects for study, 31–32

Miwi2, 141
MKLP1, 116, 123–126
MMB/dREAM1 complex, 57
MPK-1, 25
MPM2, 158
mRNA, See Messenger RNA
MSP, See Major sperm protein
MyoD, 194

N
NANOS, 4, 8, 98, 101
NANOS2, 15–16
NEB, See Nuclear envelope breakdown
NGN3, 16
NLRP2, 178
nos, translational regulation in oogenesis, 74–75
NOS2, mouse sex determination, 29
NPPC, 151
NPR2
Nuclear envelope breakdown (NEB), 157–158
Nuclear transfer, eggs and oocytes
development
abnormal outcomes
early gene expression, 190
epigenetic memory, 189–190
progressive cell differentiation, 189
normal outcomes
cancer nuclei, 188–189
cell type switching, 188
cross-species transfer, 189
eye gene expression, 188
totipotency, 187–188
experimental systems, 186
historical perspective, 187
mechanisms of somatic nucleus reprogramming to
embryo nucleus
chromatin access, 194–195
chromosomal protein exchange at mitosis, 193–194
DNA replication factor supply, 194

219
Nuclear transfer, eggs and oocytes (continued)
  molecular changes
  cell extract studies, 192–193
  chromatin condensation and protein exchange, 191–192
  DNA methylation, 190–191
  epigenetic modification, 191
  somatic mutation, 190
  telomere replacement, 191
  overview, 185–186

O
  Oct4, 190, 194
  OMA-1, 101
  OMA-2, 101
  OOC, See Oocyte-cumulus complex
  Oocyte-cumulus complex (OOC), 151

Oogenesis
  Caenorhabditis elegans
    maturation regulation by sperm, 154–156
    oocyte to zygote transition regulation, 156–157
    coordination between developmental and cell cycle control, 161
  Drosophila
    egg activation and entry into embryogenesis, 159–160
    meiotic maturation, 157–158
    metaphase I arrest and release of arrest, 158–159
    prophase I arrest, 157
  mammals
    egg activation and entry into embryogenesis, 154
    maintenance of meiotic arrest, 149–152
    meiotic maturation, 153
    metaphase II arrest and release, 153–154
    stages, 150
  meiotic arrest
    events, 149
    intercellular communication and second messengers, 161
    overview, 148–149
    reproductive strategy relationship with meiotic regulation, 160
  Piwi role, 135–136
  sex chromosome gene expression, 41–44
  translational control
    Drosophila
      caudal, 76
      grk, 75–76
      hunchback, 76
      nos, 74–75
      oskar, 72–74
    oocyte maturation, 76–77
    overview, 71–72
    polyadenylation in vertebrates, 76–79
    prospects for study, 79–80

Orb, 74
  oskar, translational regulation in oogenesis, 72–74

P
  PARn, See Poly(A) ribonuclease
  PAX6-1, 94, 102
  P-body, 92–94, 141
  Peg1, 172, 178
  Peg3, 172
  Peg10, 170
  PGC, See Primordial germ cell
  PGL-1, 94–95
  PGL-3, 95
  piRNA
    biogenesis
      ping-pong-independent generation, 139
      posttranscriptional amplification, 138–139
      precursor processing, 138
      RNA granules in formation, 98–100
    epigenetic regulation, 139–140
    identification and characterization
      Caenorhabditis elegans, 138
      insects, 136–137
      mammals, 136
      zebrafish, 137–138
      overview, 131
      prospects for study, 142
  PIWI domain proteins
    epigenetic regulation, 139–140
    germline functions
      oogenesis, 135–136
      primordial germ cell formation, 135
      spermatogenesis, 135
      overview, 132, 134
      translation and mRNA turnover regulation, 142
    transposon activity regulation, 140–141
  Piwi-interacting RNA, See piRNA
  Plagl1, 172, 177
  PLZF, 13–14
  PNG kinase complex, 159–160
  Polo, 158
  Poly(A) ribonuclease (PARN), 77–78
  Prader–Willi syndrome (PWS), 169–171, 173
  PRC1, 41, 59, 123
  PRC2, 41
  PRDM1, 13
  PRDM14, 13
  PRG-1, 99, 138
  Primordial germ cell (PGC)
    gametogenesis, 41–42
    germline stem cell derivation, 2, 4, 8
    origins, 41
  Piwi in formation, 135
PUMILO, 4, 8
PWS, See Prader–Willi syndrome

R
RA, See Retinoic acid
RBMs, See RNA-binding motifs
REDD1, 1
Retinoic acid (RA), mouse sex determination, 28–29
Ring canals, See Intercellular bridges, germ cells
RINGO, 78
RNA granules, germ cells
assembly nucleation
organelles, 95–96
proteins, 95
Tudor domain binding to methylated arginine, 96–97
conserved components and functions
protein, 87–88
RNA, 88–90
dynamics, 94–95
functions
germ cell fate specification and differentiation, 97–98
messenger RNA regulation localization, 100–101
stability, 102
translation, 101–102
mitosis and chromatin organization, 100
piRNA generation, 98–100
overview, 85
types
Balbiani body, 86
chromatid body, 92
germsplasm granules, 91–92
P-body, 92–94
perinuclear granules, 86
sponge body, 86, 90
RNA interference, See siRNA
RNA-binding motifs (RBMs), 126–127
RhlI, 170

S
Silver–Russell syndrome (SRS), 170–171
siRNA
characterization and function, 132–133
germline functions, 134
overview, 131
SLY, 45–46
Small interfering RNA, See siRNA
SMURF, 6
SNARE complex, 124
SNRPN, 172, 177
Somatic cell nuclear transfer, See Nuclear transfer, eggs and oocytes
Sperm competition, See Gamete recognition
Sperm receptor for egg jelly proteins (SuREJ), sea urchin, 205–206
Spermatogenesis
Drosophila studies
mechanisms of meiotic arrest, 58–60
meiotic arrest genes, 56–57
primary spermatocyte gene expression program, 56
tMAC complex, 57–58
intercellular bridges, 118–120
mouse studies
ACT, 61–63
CREM, 59, 61–63
KIF17b, 61–63
promiscuous transcription, 64–66
TRF2, 63–64, 66
TRF3, 63–64
overview, 55–56
Piwi role, 135
sex chromosome gene expression, 41–44
Sponge body, 86, 90
Src64, 118
SRM, See Silver–Russell syndrome
STAT, See JAK-STAT signaling
STELLA, 178
STET, 6
STRA8, mouse sex determination, 28–29
Su-bindin, See Bindin, sea urchin
SUMO-1, 45
SuREJ, See Sperm receptor for egg jelly proteins
SWITCH1, 30
SYCP3, 45

T
TAFs, See TATA-binding protein-associated factors
TA strategy, See Transit-amplifying strategy
TATA-binding protein-associated factors (TAFs), spermatogenesis role, 58–60, 65
TB-RBP, 120
Tc3, 99
TCEA2, 66
TDRD proteins, 99, 141
Tec29, 118
Telomere, somatic cell nuclear transfer effects, 191
Testis meiotic arrest (tMAC) complex, 57–58
TEX14, 121–122, 124–127
TIA-1, 97
tMAC complex, See Testis meiotic arrest complex
TPT-1, 194
Transit-amplifying (TA) strategy, germline stem cells, 2–3, 10, 16
Index

Translation
  oogenesis translational control
    *Drosophila*
  caudal, 76
  grk, 75–76
  hunchback, 76
  nos, 74–75
  oskar, 72–74
  oocyte maturation, 76–77
  overview, 71–72
  polyadenylation in vertebrates, 76–79
  prospects for study, 79–80
  Piwi protein and piRNA regulation, 142
  RNA granule regulation, 101–102
  TRF2, 63–64, 66
  TRF3, 63–64
  TSG101, 125–126
  Tudor domain, RNA granule assembly, 96–97
  Turner syndrome, 38–39

  U
  UBE3A, 172

  V
  \(\text{VAB-1}, 155\)
  \(\text{VASA}, 4, 6, 72, 94, 97, 102\)
  \(\text{VERL}, \text{See Vitalize envelope receptor for lysin}\)
  Vitalize envelope receptor for lysin
    (VERL), 208–209

  X
  X chromosome
    abnormalities and infertility, 38–41
    evolution, 37
    gametogenesis and gene expression, 41–44
    meiotic inactivation, 44–47
    reactivation and meiotic silencing as causes of infertility, 47–49

  Y
  Y chromosome
    abnormalities and infertility, 38–41
    deletions, 39
    double Y syndrome, 38–39
    evolution, 37
    gametogenesis and gene expression, 41–44
    meiotic inactivation, 44–46

  Z
  Zac1, 172
  ZFP57, 177
  Zili, 99, 137
  Ziwi, 99, 137