

Index

A

- ADAM9, 213
ADAM10, 215
ADAM17
breast remodeling role, 213, 215–216
epidermal growth factor receptor substrates, 91
knockout mouse, 77
Akt, phosphatidylinositol 3-kinase signaling, 146–147
ALD1. *See* Aldehyde dehydrogenase
Aldehyde dehydrogenase (ALD1), mammosphere enrichment, 63
Androgen receptor (AR), breast development role, 91
Apoptosis, multiphoton microscopy studies, 309
AR. *See* Androgen receptor

B

- Basement membrane. *See* Extracellular matrix
B cell, breast cancer role, 240–241
 β -Lactoglobulin (BLG), promoter for transgenic mice, 26
Bioluminescence imaging (BLI), breast cancer imaging, 300
Bissel, Mina, 132
Bittner, John J., 17
BLG. *See* β -Lactoglobulin
BLI. *See* Bioluminescence imaging
BMPs. *See* Bone morphogenetic proteins
Bone morphogenetic proteins (BMPs), ductal branching morphogenesis role, 185–186
BRCA1
knockout mouse, 34–35
mutations in breast cancer, 152–153
protein–protein interactions, 153
transgenic mouse models of breast cancer, 154–155
BRCA2
knockout mouse, 35, 153–154
mutations in breast cancer, 153
transgenic mouse models of breast cancer, 155
Breast cancer. *See also* Historical perspective, mouse mammary cancer research; Invasion; Metastasis
BRCA transgenic mouse models
BRCA1, 154–155
BRCA2, 155
breast development relevance, 187–188
cytokine signaling, 98–100

- DNA methylation studies
hypermethylated genes, 282
hypomethylated genes, 282–284
transformed breast epithelial cells, 280–282
extracellular matrix breakdown
basement membrane crossing, 114–115
in situ carcinoma, 114
metastasis, 115–116
stromal invasion, 115
density and alignment in tumor progression, 135–137
estrogen extracellular matrix assembly control and cancer implications, 135
therapeutic targeting, 116
functional genetics studies
chemotherapy studies, 271–272
gain-of-function screens, 268–269
loss-of-function screens, 265–268
phenotype defining, 270–272
prospects for study, 274
therapeutic targets
pathway gene identification, 269–270
synthetic lethal interactions, 272–274
genomic alterations associated with intrinsic subtypes
clinical utility, 255–256
metastasis, 256–258
overview, 254–255
histone modification, 286–287
human breast stem cell hierarchy in origin prediction, 66
imaging
macroscopic imaging techniques, 294–300
microscopic imaging techniques
apoptosis and therapeutic response studies, 309
fate mapping of tumor cells, 308–309
intraoperative imaging, 309–310
invasion and metastasis studies, 305–308
mammary models, 300–301
mitosis studies, 309
multiphoton microscope design and software, 301–304
types, 300
overview, 293–294
reporters and labels, 304–305

Index

- Breast cancer (*Continued*)
 immune cells in development, 234–241
 inflammation role in progression, 170, 172–173
 microenvironment. *See* Microenvironment
 oncogenes. *See specific genes*
 phosphatidylinositol 3-kinase signaling, 146–147
 stroma importance, 254
 transforming growth factor- β studies, 198–200
 tumor suppressor genes. *See specific genes*
 types
 basal-like subtype, 252–253
 claudin-low subtype, 253–254
 discovery of intrinsic subtypes, 247–250
 HER2-enriched subtype, 251–252
 luminal subtypes, 250–251
 mouse models, 27–28
- Breast development
 breast cancer relevance, 187–188
 bud maturation, 183–185
 cytokine signaling, 96–98
 duct branching morphogenesis, 185–187
 dynamic stages, 206–208
 extracellular matrix
 cell–matrix interactions
 branching ductal morphogenesis, 108–110
 ductal patterning, 111–113
 polarized mammary duct formation, 110–111
 developmental changes
 fibronectin regulation of mechanical properties, 133–135
 overview, 132–133
 hormonal control in mouse
 differential hormone action mechanisms, 78
 estrogen, 73–74
 growth hormone, 74
 overview, 72
 progesterone, 74–75
 prolactin, 74–75
 signaling, 76–78
 systemic versus local effects, 72–73
 human, 56–58
 microenvironment role, 164–166
 morphogenesis in embryos, 177–180
 placode development, 183
 prospects for study, 188
 puberty, 226–231
 specification of mammary line, 180–183
- C
CAF. *See* Carcinoma-associated fibroblast
Carcinogens, history of studies in mice, 4–5
Carcinoma-associated fibroblast (CAF), extracellular matrix changes, 136–137
Cardiff, Robert, 29
- CDK10, breast cancer studies, 272
CDKN2A, hypermethylation in breast cancer, 282
Chromatin remodeling. *See* DNA methylation; Histone modification
Collagen. *See* Extracellular matrix
Colony-stimulating factor-1 (CSF-1)
 breast cancer role, 236
 knockout mouse, 229–230
 lactation role, 232
 pubertal mammary development role, 226, 229
COX. *See* Cyclooxygenase
CpG island. *See* DNA methylation
CSF-1. *See* Colony-stimulating factor-1
Cyclooxygenase (COX), inhibitor effects on tumor progression, 170, 172
Cytokine signaling. *See* JAK/Stat signaling
- D
DCIS. *See* Ductal carcinoma in situ
Development. *See* Breast development
DNA methylation
 abundance in human genome, 278–280
 analytical techniques, 279
 breast cancer studies
 hypermethylated genes, 282
 hypomethylated genes, 282–284
 transformed breast epithelial cells, 280–282
 histone modification relationship in gene silencing, 287–288
 methyltransferases, 278
 prospects for study, 288
 transforming growth factor- β regulation, 200
Ductal branching. *See* Breast development
Ductal carcinoma in situ (DCIS)
 microenvironment abnormalities, 169
 mammary intraepithelial neoplasia outgrowth model, 32–33, 37
Dunn, Thelma, 16
Dvorak, Harol, 171
- E
E-cadherin, knockout mouse, 35–36
ECM. *See* Extracellular matrix
EGFR. *See* Epidermal growth factor receptor
EMT. *See* Epithelial-to-mesenchymal transition
Eosinophil, pubertal mammary development role, 227–228, 230
Epidermal growth factor receptor (EGFR). *See also* Erbb2
 breast development role, 90–92, 212
 ErbB family, 88
 knockout mouse, 77

- macrophage delivery of ligands in breast cancer, 237
mammary cancer development role, 93
- Epigenetics. *See* DNA methylation; Histone modification
- Epithelial cell
cell–cell interactions, 210
stem cells. *See* Human breast stem cells; Murine mammary stem cell
types in mammary gland, 208–209
- Epithelial-to-mesenchymal transition (EMT)
breast development, 187
breast epithelium, 64
history of study, 16, 20
interleukin-6 induction, 99
- ErbB2*
signaling effects on cell cycle progression and transcription factor networks, 151
transgenic mouse models, 30–31, 93, 147–149
- Estrogen
extracellular matrix assembly control and cancer implications, 135
receptor
coregulators, 79–82
knockout mice
ER α , 73–74
ER β , 74
signaling, 76–77
structure, 78–79
regulation of release, 72–73
transforming growth factor- β regulation, 197
- Ets2, PTEN effects, 171
- Extracellular matrix (ECM)
cell force
contractile pathways in generation, 128–129
measurement, 127–128
cell–matrix interactions
breakdown in breast cancer
basement membrane crossing, 114–115
in situ carcinoma, 114
metastasis, 115–116
stromal invasion, 115
breast development role
branching ductal morphogenesis, 108–110
ductal patterning, 111–113
polarized mammary duct formation, 110–111
mammary differentiation role
integrin-prolactin cross talk, 113–114
involution, 114
overview, 105–108
therapeutic targeting in cancer, 116
density and alignment in tumor progression, 135–137
hormonal control of assembly and cancer implications, 135
- mechanical properties
developmental changes
fibronectin regulation of mechanical properties, 133–135
overview, 132–133
focal complexes as mechanical sensors, 129–131
mechanical signaling regulation of proliferation and differentiation, 131–132
stiffness, 126–127
tensile force dynamics in mammary gland, 126
transforming growth factor- β regulation, 124–125
tumor invasion and mechanosignaling, 137–138
receptors on cells, 124
stromal modifiers, 212–214
synchronizing parenchymal, stromal, and extracellular matrix homeostasis, 218
transforming growth factor- β response, 196
- F**
- FAK. *See* Focal adhesion kinase
- FGFs. *See* Fibroblast growth factors
- Fibroblast growth factors (FGFs)
breast development role, 77, 90–91, 212
receptors
mammary cancer development role, 92–94
types and ligands, 88–89
specification of mammary line, 180–182
- Fibronectin (FN), regulation of extracellular matrix mechanical properties, 133–135
- Filamin, mechanical sensor, 11
- Fluorescence molecular tomography (FMT), breast cancer imaging, 296, 300, 304
- FMT. *See* Fluorescence molecular tomography
- FN. *See* Fibronectin
- Focal adhesion kinase (FAK)
cell contraction regulation, 129
mechanical sensor, 131
tumor invasion role, 137
- FSP1, stromal fibroblast function, 171
- G**
- Gain-of-function screens, breast cancer, 268–269
- GATA-3
breast development role, 96–97, 212
mammary stem cell regulation in mouse, 50
- GH. *See* Growth hormone
- Growth hormone (GH)
breast development role, 91, 211
receptor knockout mouse, 74
regulation of release, 72–73

Index

H

- Halberg, Franz, 17
HAN. *See* Hyperplastic alveolar nodule
Hedgehog, mammary stem cell signaling in mouse, 50
HIM xenograft. *See* Human in mouse (HIM) xenograft
Histology, mammary gland, 208–210
Histone modification
 breast cancer versus normal epithelial differentiation, 286–287
 combinatorial variations associated with gene transcription, 284–286
DNA methylation relationship in gene silencing, 287–288
prospects for study, 288
Historical perspective, mouse mammary cancer research
 carcinogen studies, 4–5
 early years, 1–2, 14–16
 first description, 14–15
 genetic studies, 4
 hormone studies, 2–3
 human significance, 9–10, 20–21
 inbred mouse studies, 17
 mammary stem cells, 18–19, 41–42
 mouse mammary tumor virus studies, 3–5, 8, 13–14, 17–18
 pathobiology of tumorigenesis, 5–7
 timeline, 15
 transplantation studies, 7–9, 18–19
Human breast stem cell
 breast development, 56–58
 cell line studies, 60–62
 chemotherapy effects on cancer stem cells, 155–156
 cytokeratin staining patterns in normal and neoplastic breast tissue, 59–60
 epithelial stem cell
 identification, 62–63
 profiling, 64–66
 hierarchy in breast cancer origin prediction, 66
 histone modification, 286
 mammary remodeling role, 214–215
 mammosphere culture, 63–64
 metastasis genomics studies, 259
 primary culture studies, 58–59
Human in mouse (HIM) xenograft, history of study, 8–9
Hyperplastic alveolar nodule (HAN), history of study, 6–7

I

- IGFs. *See* Insulin-like growth factors
IKBKE, breast cancer studies, 268
IL-6. *See* Interleukin-6
ILC. *See* Invasive lobular carcinoma
Inbred mouse strains, origins, 14, 16

- Inflammation, tumor progression role, 170, 172–173
Insulin, receptor, 90
Insulin-like growth factors (IGFs)
 binding proteins, 90, 94, 270
 breast development role
 IGF-1, 90–91, 211
 IGF-2, 78
 mammary cancer development role, 93–94
 receptors, 89–90
Integrins
 oncogene cross talk in mammary tumor progression, 150–151
 prolactin cross talk in mammary differentiation, 113–114
Interleukin-6 (IL-6), breast cancer role, 98
Invasion
 cell–matrix interactions, 115
 extracellular matrix mechanosignaling, 137–138
 multiphoton microscopy studies, 305–306
Invasive lobular carcinoma (ILC), E-cadherin knockout mouse, 35–36
Involution
 cell–matrix interactions, 114
 immune cell function, 214, 232–234
 mechanisms, 208

J

- JAK/Stat signaling
 cytokine receptor families, 95–96
 mammary cancer development role, 95, 98–100
Stats
 breast cancer role, 98–100
 breast development role, 96–98
 types, 96

K

- Keratin-5, staining patterns in normal and neoplastic breast tissue, 59–60
Keratin-14
 promoter for transgenic mice, 29
 staining
 breast development, 56–57
 patterns in normal and neoplastic breast tissue, 59
Keratin-19, staining
 breast development, 56–57
 patterns in normal and neoplastic breast tissue, 59–61
Kinesins, breast cancer expression studies, 269
Knockout mouse
 ADAM17, 77
 BRCA1, 34–35
 BRCA2, 35, 153–154

colony-stimulating factor-1, 229–230
E-cadherin, 35–36
epidermal growth factor receptor, 77
estrogen receptor
 ER α , 73–74
 ER β , 74
growth hormone receptor, 74
Lef1, 183
leptin, 76
Lrp6, 186
Msx2, 187
overview of tumor suppressor gene knockout,
 29–30, 33
progesterone receptor, 74
prolactin receptor, 74
PTEN, 147
TP53, 33–34
transforming growth factor- β , 170, 198
K-Ras, synthetic lethality targeting of mutants,
 273–274
Kuperwasser, Charlotte, 167

L

Lactation. *See also* Prolactin
 leukocyte function, 231–232
 progesterone role, 207–208
Lathrop, Abbie, 16
LCIS. *See* Lobular carcinoma in situ
Lef1
 knockout mouse, 183
 mammary bud development role, 184
 placode development role, 183
Leptin, knockout effects on breast development, 76
Little, Clarence Cook, 1, 16–17
Lobular carcinoma in situ (LCIS), 36
Loss-of-function screens, breast cancer, 265–268
Lrp6, ductal branching morphogenesis role, 185
Lyden, David, 167

M

Macrophage
 breast cancer role, 236–237
 involution role, 233
 lactation role, 232
 mammary remodeling role, 214
 pubertal mammary development, 226–228
Magnetic resonance imaging (MRI), breast cancer
 imaging, 294, 296, 304–305
Mammary bud, maturation, 183–185
Mammary Imaging Window (MIW), 301–302
Mammary intraepithelial neoplasia outgrowth (MINO)
 model, 32–33, 37
Mammosphere culture, human breast stem cells,
 63–64

Mast cell
 lactation role, 232
 pubertal mammary development role, 230
Matrix metalloproteinases (MMPs)
 mammary remodeling role, 213–214
 master signals, 216–218
 paracrine signaling, 215–216
 synchronizing parenchymal, stromal, and
 extracellular matrix homeostasis, 218
tissue inhibitors, 213
tumor microenvironment facilitation, 218–219
types and sources in mammary gland, 213
MDM2
 inhibitors, 272
 p53 interactions, 151–152
Metastasis
 cell–matrix interactions, 115–116
 genomic alterations associated with intrinsic breast
 cancer subtypes, 256–258
 mouse mammary tumors, 20
 multiphoton microscopy, 305–308
Methylation-specific digital karyotyping (MSDK), 279
Microenvironment
 breast development role, 164–166
 matrix metalloproteinases and tumor
 microenvironment facilitation, 218–219
 nonmammary stem progenitor cell regulation, 49
 prospects for study, 173
 tumor abnormalities
 clinical relevance in tumorigenesis, 171–173
 functional relevance in tumorigenesis, 169–170
 metastasis, 166–169
 tumor mouse models, 36, 170–171
MINO model. *See* Mammary intraepithelial neoplasia
 outgrowth (MINO) model
MIW. *See* Mammary Imaging Window
MLC. *See* Myosin light chain
MMPs. *See* Matrix metalloproteinases
MMTV. *See* Mouse mammary tumor virus
Mouse mammary tumor virus (MMTV)
 carcinogen interactions, 5
 history of study, 3–5, 8, 13–14, 17–18
 insertion sites, 18
 promoter for transgenic mice, 26, 29, 31, 147–149
MPM. *See* Multiphoton microscopy
MRI. *See* Magnetic resonance imaging
MSDK. *See* Methylation-specific digital karyotyping
Msx1, mammary bud development role, 185
Msx2, mammary bud development role, 185, 187
Multiphoton microscopy (MPM)
 advantages, 300
 breast cancer applications
 apoptosis and therapeutic response studies, 309
 correlating tumor cell behavior with gene
 expression and markers of metastatic risk,
 306, 308

Index

- Multiphoton microscopy (MPM) (*Continued*)
fate mapping of tumor cells, 308–309
intraoperative imaging, 309–310
invasion and metastasis, 305–307
mitosis studies, 309
microscope design, 301–303
reporters, 304
software for 4D imaging, 302–303
techniques, 300–301
- Murine mammary stem cell
epithelial cell hierarchy
hormonal regulation, 47
overview, 45–47
parity-identified cells, 47–48
history of study, 18–19, 41–42
isolation, 43–45
mammary remodeling role, 214–215
markers, 55
morphological evidence in epithelium, 42–43
nonmammary stem progenitor cell regulation by microenvironment, 49
prospects for study, 50–51
regulators, 49–50
template DNA selective segregation, 48–49
- Myeloid suppressor cells, breast cancer role, 237
- Myosin light chain (MLC), cell contraction, 129
- N**
- Notch, mammary stem cell signaling in mouse, 50
- Nutlin-3, breast cancer studies, 272
- O**
- Oncogenes. *See specific genes*
- P**
- p53
cell cycle regulation, 151–152
gene. *See TP53*
mammary stem cell self-renewal role in mouse, 50
MDM2 interactions, 151–152
- p130Cas, mechanical sensor, 129–131
- PAK-1, SRC-3 as substrate, 81
- Parathyroid hormone-related protein (PTHrP)
ductal branching morphogenesis role, 185–186
mammary bud development role, 184, 211
- PARP. *See Poly(ADP-ribose) polymerase*
- PET. *See Positron emission tomography*
- Phosphatidylinositol 3-kinase (PI3K), signaling in cancer, 146–147
- PI3K. *See Phosphatidylinositol 3-kinase*
- Pierce, Barry, 19
- PITX1, breast cancer studies, 270–271
- Placode, development, 183, 212
- Pollard, Jeff, 171
- Poly(ADP-ribose) polymerase (PARP), inhibitor sensitization via BRCA deficiency, 155
- Positron emission tomography (PET), breast cancer imaging, 294, 296, 304
- Progesterone
lactation role, 207–208
receptor
coregulators, 79–82
estrogen induction, 211
knockout mouse, 74
signaling, 77–78
structure, 78–79
regulation of release, 72–73
- Prolactin
integrin-prolactin cross talk in mammary differentiation, 113–114
receptor
knockout mouse, 74
signaling, 77–78
regulation of release, 72–73
- PTEN
Ets2 effects, 171
knockout mouse, 147
loss in breast cancer, 64, 66
phosphatidylinositol 3-kinase antagonism, 146
- PTHrP. *See Parathyroid hormone-related protein*
- R**
- Radiation, history of cancer induction studies, 5
- RANKL, signaling in breast development, 77–78
- RB. *See Retinoblastoma protein*
- Remodeling, mammary gland. *See also Matrix metalloproteinases*
epithelial morphogens and inhibitors, 211–212
immune cells, 214
master signals, 216–218
paracrine signaling, 215–216
stem cells, 214–215
stromal extracellular matrix modifiers, 212–214
synchronizing parenchymal, stromal, and extracellular matrix homeostasis, 218
systemic mammogens, 210–211
- REST, breast cancer studies, 271
- Retinoblastoma protein (RB), cell cycle regulation, 151
- Rho
cell contraction regulation, 129
mammary bud development role, 184
- RNA interference, screens in breast cancer, 265–270
- ROCK, cell contraction regulation, 129
- S**
- SDPP. *See Stroma-derived prognostic predictor*
- Sgroi, Dennis, 168

ShcA, signaling in tumor progression, 150
Single Sample Predictor (SSP), 248
SMADs, transforming growth factor- β signaling, 192–194
Snell, George, 17
c-Src, signaling in tumor progression, 150
SRC coactivators
 SRC-3 level and activity regulation, 80–82
 steroid hormone receptor regulation, 80
SSP. *See* Single Sample Predictor
Stat. *See* JAK/Stat signaling
Stem cell. *See* Human breast stem cell; Murine mammary stem cell
Stevens, Roy, 19
Stroma-derived prognostic predictor (SDPP), 172
Synthetic lethality, breast cancer studies, 272–274

T

TACS. *See* Tumor associated collagen signatures
Talin, mechanical sensor, 129–130
Tbx3, deficiency and ulnar-mammary syndrome, 182
T cell, breast cancer role, 238–240
TDLU. *See* Terminal ductal-lobular unit
TEB. *See* Terminal end bud
Terminal ductal-lobular unit (TDLU), 56, 238
Terminal end bud (TEB), development, 77, 90–92, 133, 206, 208–210, 213, 227–231
TGF- β . *See* Transforming growth factor- β
TIMPs. *See* Matrix metalloproteinases
TP53
 knockout mouse, 33–34
 mutations in cancer, 152
Transforming growth factor- β (TGF- β)
 activation, 192
 breast cancer studies, 198–200
 breast development role, 207, 212
 breast remodeling role, 212, 216
 epigenetic regulation, 200
 estrogen regulation, 197
 extracellular matrix response, 196
 human breast stem cell signaling, 66

knockout mouse, 170, 198
mammary distribution, 195–196
prospects for study, 200–201
receptors, 192, 198–199
signaling, 192–194
transgenic mice, 196–197
Transgenic mouse
 BRCA mutant models of breast cancer
 BRCA1, 154–155
 BRCA2, 155
 ErbB2 models, 30–31, 93, 147–149
 mammary-specific promoters, 26, 29
 transforming growth factor- β , 196–197
Transplantation models
 historical perspective, 7–9, 18–19
 human in mouse xenograft, 8–9
 overview, 31–32
Tumor associated collagen signatures (TACS), 136
Tumor suppressor genes. *See specific genes*
TWIST, epithelial-to-mesenchymal transition mediation, 99
Two-photon microscopy. *See* Multiphoton microscopy

V

Vascular endothelial growth factor (VEGF)
 matrix metalloproteinase regulation, 216
 metastasis genomics signature, 258–259
 myeloid cell delivery, 236
VEGF. *See* Vascular endothelial growth factor

W

WAP. *See* Whey acidic protein
Whey acidic protein (WAP), promoter for transgenic mice, 26
Wnt
 mammary bud development role, 184, 186
 mammary stem cell signaling in mouse, 50
 placode development role, 183
 specification of mammary line, 180