Index

A
ACTA2, smooth muscle vasculopathy mutations, 163
ACTC1, cardiomyopathy mutation, 141
Activin A, 72
ADAMTS1, 96
Aortic aneurysm
gene mutations
extracellular matrix, 157
table, 155–156
Loeys–Dietz syndrome and transforming growth factor-β signaling mutations, 159–160
Marfan syndrome
aneurysm and gene mutations, 154, 156
transforming growth factor-β signaling,
157–159
pathophysiology, 153–154
prospects for study, 165
smooth muscle vasculopathy, 162–164
transforming growth factor-β signaling
canonical versus noncanonical signaling,
160–162
high versus low, 164–165
Aortic arch, artery patterning, 59–60
Arrhythmogenic right ventricular cardiomyopathy (ARVC)
clinical features and gene mutations, 139
human pluripotent stem cell models, 193, 198
Arterial pole, progenitor cells, 5–6
ARVC. See Arrhythmogenic right ventricular cardiomyopathy
ASD. See Atrial septal defect
Atrial septal defect (ASD), gene mutations, 109, 111–112, 122
Atrioventricular septal defect (AVSD)
copy number variation, 125–126
gene mutations, 109, 111–112, 123
AVSD. See Atrioventricular septal defect

B
Ballooning morphogenesis, biomedical impact, 21
β-catenin
mesoderm differentiation, 70–71
venous pole development, 18
BMPs. See Bone morphogenetic proteins
Bone morphogenetic proteins (BMPs)
cardiogenic mesoderm precursors, 52–55
chamber morphogenesis, 20
endothelial cell differentiation from stem cells, 72
epicardium formation, 55
second heart field development, 18, 20
venous pole development, 7, 18
Boolean models, heart development, 36, 38
Brachyury, 52

C
Cardiac crescent. See First heart field
Cardiac neural crest cell (CNCC)
aortic arch artery patterning and outflow tract
septation, 59–60
induction and migration signaling, 57–59
progenitor cells, 50–52, 57
valve development, 90, 92
Cardiac stem cell. See Human pluripotent stem cell
Cardiomyocyte
regenerative models
cell lines, 172–173
coculture, 171–172
microfluidic systems, 172
overview, 170–171
primary cells, 173
stem/progenitor cell differentiation, 173–174
three-dimensional culture, 171
two-dimensional culture, 171
stem cell differentiation in vitro, 69–71
stem cell models of heart disease. See Human
pluripotent stem cell
Cardiomyopathy
classification, 134
gene mutations
arrhythmic syndromes, 140
arrhythmogenic right ventricular
cardiomyopathy, 139
dilated cardiomyopathy, 138–139
discovery, 134–135
hypertrophic cardiomyopathy, 135
left ventricular compaction, 139–140
novel variants in general population, 141–142
restrictive cardiomyopathy, 140
table, 136–138
therapy guidance, 147
genetic models
development, 142–143
functional evaluation
Cardiomyopathy (Continued)
induced pluripotent stem cells, 145
zebrafish, 145–146
 genetic testing, 147
human pluripotent stem cell models, 192
nongenetic factors, 143–145
overlapping phenotypes and genes, 140–141
overview, 133–134
prospects for study, 147–148
reprogramming for regenerative medicine
clinical prospects, 223
fibroblast reprogramming, 218–219
functional comparison to cardiomyocytes, 219–220
mouse studies, 220–222
overview, 217–218
Catecholaminergic polymorphic ventricular tachycardia (CPVT), human pluripotent stem cell models, 191–192, 198
Cathepsin K, valve remodeling, 95
Chamber morphogenesis
epicardium-derived cells, 55, 57
initiation, 20–21
CHD. See Congenital heart disease
Chromatin modification. See Epigenetics
Clopidogrel, pharmacogenomics, 230–231
CNCC. See Cardiac neural crest cell
CNV. See Copy number variation
COL3A1, Marfan syndrome mutations, 154
COL6A1, modifier gene in congenital heart disease, 123
COL6A2, modifier gene in congenital heart disease, 123
Compact layer, cell lineages, 8
Conduction system, cell lineages, 8–9
Congenital heart disease (CHD). See also specific genes
copy number variation, 124–127
denovo mutations, 124
epidemiology, 107, 121
genome-wide association study of common variants, 126, 128–129
modifier genes, 115, 122–124
monogenic gene mutations, 60, 107–114
noncoding mutations, 129–130
phenotypic variability, 115–116
prospects for study
monogenic disease, 116
polygenic disease, 130–131
TBX mutations, 114–115
Copy number variation (CNV), congenital heart disease, 124–126
CPVT. See Catecholaminergic polymorphic ventricular tachycardia
CRELD1, modifier gene in congenital heart disease, 115, 123
CRISPR/Cas9 technology, genome-wide screening of diploid stem cells, 75–78, 278
CYP2C9, 229–230
CYP2C19, 230–231

 D
DCM. See Dilated cardiomyopathy
DES, cardiomyopathy mutation, 140
DICER, 41
DiGeorge syndrome, 5, 20, 60, 11
Dilated cardiomyopathy (DCM)
clinical features and gene mutations, 138–139
human pluripotent stem cell models, 192
DNA methylation. See Epigenetics
Down syndrome (DS), congenital heart disease, 114–115, 123, 126
Drug discovery and development
animal models, 269–272
cardiovascular disease mortality, 263–264
clinical trials, 272–274
ischemia reperfusion injury, 270
portfolio decisions for target selection, 266–269
regenerative models
drug-screening tools, 252–253
human pluripotent stem cell heart disease models, 253–255
overview, 251–252
prospects, 259
regenerative therapy
overview, 256
mesenchymal stem cells, 256–257
paracrine factors and developmental pathway modulators, 257–259
toxicoology and safety assays, 255
research and development overview, 264–266
DS. See Down syndrome

 E
EB. See Embryoid body
EC. See Endothelial cell
ECM, see Extracellular matrix
ELN
aortic aneurysm gene mutations, 157
modifier gene in congenital heart disease, 122–123
Embryoid body (EB), cardiomyocyte differentiation in vitro, 70
Embryonic stem cell. See Human pluripotent stem cell
EMT. See Epithelial-to-mesenchymal transition
ENCODE, 32, 120, 130
Endocardium, development, 9–10
Endothelial cell (EC)
heart valve
functions, 86–87
fusion, 94–95
human pluripotent stem cell differentiation, 196–197
stem cell differentiation in vitro, 71–72
Endothelin, 59
Epicardium
  development, 10
  proepicardium. See Proepicardium
Epicardium-derived cell (EPDC)
  cardiac injury response, 257
  heart development overview, 55, 57
  valve development, 90
Epigenetics
  gene regulatory network and cell fate attractors, 28–29
  heart development regulation, 38–40
Epithelial-to-mesenchymal transition (EMT)
  epicardium, 55
  heart valve, 88–89
  Mesp1 activation, 2
ERK1, 162
ERK2, 162
Erv2, endocardium development, 9
ETS2, fibroblast reprogramming into cardiac progenitors, 202
Extracellular matrix (ECM)
  aortic aneurysm gene mutations, 157
  heart valve
    overview, 85–86
    remodeling, 96
  scaffold materials, 241

F
FANTOM, 32
FBLN2, modifier gene in congenital heart disease, 123
FBN1
  aortic aneurysm gene mutations and alleles,
  157–158
  Marfan syndrome mutations, 154, 156–157
FGFs. See Fibroblast growth factors
FHF. See First heart field
Fibrillin-1. See FBN1
Fibroblast, reprogramming into cardiac progenitors, 202, 219
Fibroblast growth factors (FGFs)
  cardiogenic mesoderm precursors, 52–55
  chamber morphogenesis, 20, 59
  endothelial cell differentiation from stem cells, 72
  epicardium formation, 55
  Fgf10, head skeletal muscle expression, 19
  second heart field development, 5–6
  venous pole development, 7
Fibulin-4, aortic aneurysm role, 157–158
Fibulin-5, aortic aneurysm role, 157
First heart field (FHF)
  attractor states, 37
  developmental overview, 29–30, 50
  markers, 3
  mesoderm progenitors, 52, 54–55
  progenitor isolation in mice, 68
  signal gating of enhancer function, 36, 38
FOXC2, 18
FRZB, modifier gene in congenital heart disease, 123

G
GATA4
  cardiac kernel, 31
  fibroblast reprogramming, 219
  gene mutation and congenital heart disease, 60,
  111–114
  heart tube development, 16
  mesoderm progenitors, 54
  modifier genes, 115
  subpharyngeal cardiac progenitor cell proliferation
  and differentiation, 18
GATA5, modifier gene in congenital heart disease, 123
Gene regulatory network (GRN)
  epigenetic memory and cell fate attractors, 28–29
  network view of biology, 29
  overview, 26
  regulation in heart development
    Boolean models of heart development, 36, 38
    Drosophila model, 34–35
    enhancers
      functions, 33–34
      machine learning for classification, 34
      signal gating, 35–36
    prospects for study, 42–43
    restriction of developmental potential and cell
    fate, 28
  Genome editing, human pluripotent stem cells, 72–73
GLA, cardiomyopathy mutation, 135
GLP-1. See Glucagon-like peptide-1
Glucagon-like peptide-1 (GLP-1), 255
GRN. See Gene regulatory network

H
HCM. See Hypertrophic cardiomyopathy
HCN4, cardiac crescent marker, 3
Heart valve
  cell types
    endothelial cell, 86–87
    interstitial cell, 87
  development
    overview, 87–88
  patterning and epithelial-to-mesenchymal
  transition, 88–89
  extracellular matrix, 85–86
  morphogenesis
    endothelial cell fusion, 94–95
    lineage tracing
      atrioventricular valves, 90–93
      SL valves, 95–94

© 2015 by Cold Spring Harbor Laboratory Press. All rights reserved.
Heart valve (Continued)
overview, 89–90
postfusion morphogenesis, 95
prefusion of mesenchyme structures, 90
prospects for study, 99–100
remodeling
extracellular matrix, 96
lineage diversification, 95–96
structure and function, 83–85
tissue engineering
challenges, 99
ingenring in situ with scaffolds, 98–99
overview, 96–97
scaffolds, 97–98
stem cell sources, 97
Hedgehog, second heart field development, 18, 20
Hey1, heart valve development, 89
Hey2, heart valve development, 89
Histone modification. See Epigenetics
hPSC. See Human pluripotent stem cell
Human pluripotent stem cell (hPSC)
cardiomyocyte differentiation in vitro, 69–71
cardiomyopathy evaluation with induced pluripotent stem cells, 145
endothelial cell differentiation in vitro, 71–72
generation, 69
genome editing, 72–73
genome-wide screening
diploid cells
CRISPR/Cas9 technology, 75–78
prospects for cardiogenesis studies, 78
haploid cells, 73–75
heart disease models
cardiovascular progenitor cell differentiation
advances and challenges, 189
cardiomyocyte heterogeneity, 195–196
cardiomyocyte maturation, 189
interline variability in cardiac differentiation, 196
diseases, 190–194, 198
embryonic stem cell models, 197–198
induced pluripotent stem cell models, 197–198
limitations, 202–203
prospects
complex disease modeling, 198–199
personalized medicine, 201
progenitor purification and lineage marking, 199–200
tissue engineering, 200–201, 243–246
somatic cell reprogramming, 201–202
vascular smooth muscle cell and endothelial cell differentiation, 196–197
properties, 187–189
regenerative medicine, 60–61
regenerative medicine. See Regenerative models
Hutchinson–Gilford progeria, human pluripotent stem cell models, 194
Hypertrophic cardiomyopathy (HCM)
clinical features and gene mutations, 135, 142, 163
human pluripotent stem cell models, 192
I
IL-6. See Interleukin-6
Induced pluripotent stem cell. See Human pluripotent stem cell
Interleukin-6 (IL-6), inhibitors, 271
Internal ribosome entry site (IRES), 72
Interstitial cell, heart valve, 87
Interventricular septum, cell lineages, 8
IRES. See Internal ribosome entry site
Ischemia reperfusion injury, 270
Isll
arterial pole development, 5–6
cardiac kernel, 31
conduction system, 9
endocardium development, 9
epicardium development, 10
head skeletal muscle expression, 19
mesoderm progenitors, 54
second heart field expression, 4, 68
subpharyngeal cardiac progenitor cell proliferation and differentiation, 18
venous pole development, 7
J
JNK1, 162
K
Kabuki syndrome, 124
L
LAMP2, cardiomyopathy mutation, 135
Latent transforming growth factor-β-binding proteins (ITBPs), 158
LDS. See Loesv–Dietz syndrome
Left ventricular compaction (IVNC), clinical features and gene mutations, 139–140
LEOPARD syndrome, human pluripotent stem cell models, 193, 198
LHX3a, cardiac kernel, 31
LMNA, cardiomyopathy mutation, 134, 138, 141
Loesv–Dietz syndrome (LDS), transforming growth factor-β signaling mutations, 159–160
Long intergenic noncoding RNA, heart development regulation, 42
Long noncoding RNA, heart development regulation, 41
Long QT syndrome (LQTS)
- drug development, 269
- human pluripotent stem cell models, 190–191, 198

LQTS. See Long QT syndrome

LTBPs. See Latent transforming growth factor-β-binding proteins

LVNC. See Left ventricular compaction

M

MAML3, common variants, 128–129

Marfan syndrome
- aneurysm and gene mutations, 154, 156
- mitogen-activated protein kinase signaling, 162
- transforming growth factor-β signaling, 157–159, 161

Mef2C
- cardiac kernel, 31
- enhancer function, 33
- fibroblast reprogramming, 219
- subpharyngeal cardiac progenitor cell proliferation and differentiation, 18

MEIS1, 40

MEIS2, 40

Mesenchymal stem cell (MSC)
- heart valve engineering, 97
- regenerative medicine, 256–257

Mesoderm progenitors
- early vertebrate cardiogenesis, 51–52
- induction, 52

MESPI
- cardiac kernel, 31
- cardiac precursor cell expression, 5
- conduction system, 8–9
- delamination role, 2
- fibroblast reprogramming into cardiac progenitors, 202
- head skeletal muscle expression, 5
- heart tube development, 16
- mesodermal progenitors, 52

MESP2, delamination role, 2

Messenger RNA. See Synthetic chemically modified messenger RNA

Mibebradil, 271

MicroRNA
- cardiomyopathy studies, 143–144
- heart development regulation, 40–41

Mixl1, 73, 238

MLC. See Myosin light chain

modRNA. See Synthetic chemically modified messenger RNA

MSC. See Mesenchymal stem cell

MYBPC3, cardiomyopathy mutation, 135, 142

Myf5, 5

MYH11, smooth muscle vasculopathy mutations, 163

MYH7, cardiomyopathy mutation, 134–135, 139–142

MYL2, 140, 220

MYL3, 140

Myocardial tissue engineering. See Tissue engineering

MyoD, 5, 19, 218

Myosin light chain (MLC), modifications and smooth muscle vasculopathy, 162

N

Neuregulin-1, 177

NKX2-5
- conduction system, 9
- endocardium development, 9
- enhancer function, 33, 36
- epicardium development, 10
- fluorescent protein fusion, 73
- gene mutation and congenital heart disease, 60, 108–111
- heart tube development, 16
- mesoderm progenitors, 54, 238
- modifier genes, 115
- subpharyngeal cardiac progenitor cell proliferation and differentiation, 18
- venous pole development, 7

Notch, chamber morphogenesis, 20

NOTCH1
- cardiomyopathy mutation, 144
- valve development, 95

O

OCT4, cardiac kernel, 31

OFT. See Outflow tract

Outflow tract (OFT)
- gene mutations and defects, 5
- septation, 59–60

P

PE. See Proepicardium

PEO. See Proepicardial organ

Personalized medicine
- cardiovascular risk prediction, 227–229
- genome-wide association studies, 226–227
- human pluripotent stem cell heart disease models, 201
- next-generation sequencing, 227

pharmacogenomics
- clopidogrel, 230–231
- statins, 231
- warfarin, 229–230
- prospects, 231–232

Pharmacogenomics. See Personalized medicine

Pitx2
- cardiac patterning, 19
- heart valve development, 88
Index

PLN, cardiomyopathy mutation, 141
Pol II. See RNA polymerase II
Pompe’s disease, human pluripotent stem cell models, 193
PRDM16, cardiomyopathy mutation, 139
PRKAG2, 135
Proepicardial organ (PEO), epicardium development, 10
Proepicardium (PE)
chamber maturation and coronary vessel formation, 55, 57
epicardium-derived cells, 55, 57
induction, 55
origin and fates, 55–56
progenitor cells, 51
PTPN11, common variants, 129
Pum1, 74

R
RANKL, valve remodeling, 95
RCT. See Reverse cholesterol transport
Regenerative models
animal models
amphibians, 176
humans, 179
large animals, 178
noncardiac models, 174
small mammals, 176–178
snake, 176
species comparison of heart characteristics, 176–178
zebrafish, 175–176
cell models
cardiomyocyte, 170–171
cell lines, 172–173
coculture, 171–172
microfluidic systems, 172
primary cells, 173
stem/progenitor cell differentiation, 173–174
three-dimensional culture, 171
two-dimensional culture, 171
computational models, 170
drug discovery and development
drug-screening tools, 252–253
human pluripotent stem cell heart disease models, 253–255
overview, 251–252
prospects, 259
regenerative therapy
overview, 256
mesenchymal stem cells, 256–257
paracrine factors and developmental pathway modulators, 257–259
toxicology and safety assays, 255

overview, 169–170
schematic of complexity, 170
tissue models, 174
whole heart/ex vivo models, 174
Restrictive cardiomyopathy, clinical features and gene mutations, 140
Reverse cholesterol transport (RCT), 255
Right ventricle (RV), gene mutations and defects, 5
RNA polymerase II (Pol II), epigenetic regulation of heart development, 38, 40
RV. See Right ventricle

S
SCF. See Stem cell factor
SCN10A, 34
SCN5A, 34
SDF-1, cardiac regeneration studies, 258
Second heart field (SHF)
attractor states, 37
developmental overview, 29–30, 50
diversity encoding, 18–19
gene mutations and disease, 19–20
Isli, 4–6, 68
mesoderm progenitors, 52, 54–55
progenitor cells, 5–6, 16–17
progenitor isolation in mice, 68
signal gating of enhancer function, 36, 38
Selector gene hypothesis, 26–28
SGS. See Shprintzen–Goldberg syndrome
SHF. See Second heart field
Shprintzen–Goldberg syndrome (SGS), 165
Sinus venosus, formation, 7
SKI, 165
SLCO1B1, 231
SMAD2, de novo mutations, 124
SMAD3, Loeys–Dietz syndrome mutations, 159–160, 164
SMAD4, aortic aneurysm gene mutations, 160
SMARCD3, heart tube development, 16
Smooth muscle cell, human pluripotent stem cell differentiation, 196–197
Smooth muscle vasculopathy (SMV), aortic aneurysm, 162–164
SMV. See Smooth muscle vasculopathy
SSEA-1, 178
Statins
drug discovery and development, 263, 272
pharmacogenomics, 231
Stem cell. See Human pluripotent stem cell; Mesenchymal stem cell
Stem cell factor (SCF)
cardiac regeneration studies, 258
endothelial cell differentiation from stem cells, 72
Synthetic chemically modified messenger RNA (modRNA) advantages and limitations versus conventional gene transfer, 211 heart progenitor cell fate studies, 210–211 immune surveillance escape for protein expression, 208–209 overview, 207–208 therapeutic application, 211, 213, 279 transfection of cardiac and skeletal muscle cells, 209–210

Systems biology
genome-wide technology, 31–32 network view of biology, 29 overview, 25–26

T
TALENs, 75, 146, 197
TB4, cardiac regeneration studies, 258–259

TBX1
arterial pole development, 5–6
defects and heart development, 5, 20
gene mutation and congenital heart disease, 60, 114–115
head skeletal muscle expression, 19
subpharyngeal cardiac progenitor cell proliferation and differentiation, 18

TBX2
chamber morphogenesis, 21
heart valve development, 89

TBX3, chamber morphogenesis, 21

TBX5
cardiac crescent marker, 3
cardiac kernel, 31
chamber morphogenesis, 21
fibroblast reprogramming, 219
gene mutation and congenital heart disease, 60, 114
heart tube development, 16
noncoding mutations, 129–130
second heart field expression, 5, 238

TBX6, cardiac kernel, 31
Tbx18, epicardium development, 10

TBX20

cardiac kernel, 31
chamber morphogenesis, 21

Tetralogy of Fallot (TOF), 121, 125, 129
TGF-β. See Transforming growth factor-β

Timothy syndrome, human pluripotent stem cell models, 191

Tissue engineering. See also Regenerative models; specific tissues
functional myocardium applications

drug testing
advantages and limitations, 243
cardiotoxicity, 242
proarrhythmic actions, 242–243
human pluripotent stem cell heart disease models, 200–201, 243–246
heart cells, 237–239
overview, 235–237
scaffold materials, 240–242
TOF. See Tetralogy of Fallot

TPM1, cardiomyopathy mutation, 140

Trabeculated myocardium, cell lineages, 8

Transforming growth factor-β (TGF-β), aortic aneurysm signaling
canonical versus noncanonical signaling, 160–162
high versus low levels of signaling, 164–165
Loeys–Dietz syndrome defects, 159–160
Marfan syndrome, 157–159, 161

TTN, cardiomyopathy mutation, 139, 141–142

V

Valve. See Heart valve

Vascular endothelial growth factor (VEGF)
cardiac regeneration studies, 258–259
endothelial cell differentiation from stem cells, 72
synthetic chemically modified messenger RNA studies of cell fate, 210–212

VEGF. See Vascular endothelial growth factor

VEGFR2
cardiac crescent and linear heart tube formation, 52, 54–55
mesoderm progenitors, 54
Venous pole, progenitor cells, 6–8

Ventricular septal defect (VSD)
gene mutations, 108–109, 111–112, 122
phenotypic variability, 115–116

VKORC1, 229–230

VSD. See Ventricular septal defect

W

Waddington landscape, 26–27

Warfarin, pharmacogenomics, 229–230

WES. See Whole exome sequencing

Whole exome sequencing (WES), cardiomyopathy studies, 141, 147a
Williams syndrome, human pluripotent stem cell models, 194

WNT

cardiogenic mesoderm precursors, 52
venous pole development, 18

Wnt1, epicardium development, 10, 55