CAMBRIDGE

Cambridge University Press
978-0-521-89628-3 - Cancer Stem Cells
Edited by William L. Farrar
Index
More information

Index

ABCB5 drug efflux transporter, 40–41
  expression in melanoma stem cells
ABCG2+ Du145 cells
ABCG2 MDR transporter, 22, 40
AC133 monoclonal antibody, 4
activins (TGF-β–related proteins), 140–141
acute lymphoblastic leukemias (ALLs)
  identical twin studies, 96
  LSC populations in, 94
acute myeloid leukemia (AML), 3, 17, 72, 75–76 . *See also* leukemic stem cells
  $CD34^+CD38^-$ cells, 2, 5, 94
  first CSCs isolation from, 17
  FLT3 testing for, 76
  lesion classes I/II, 75
  response to cyclic chemotherapy, 77–78
  stages of maturation arrest, 72
  21-kDa guanine-nucleotide binding protein mutation, 76
acute promyeloid leukemia (APL)
  retinoic acid (RA) treatment for, 74–75
  stages of maturation arrest, 72
ADAM (A Disintegrin And Metalloproteinase) mediated cleaveage, 133
Al-Hajj, M., 7–9
all-trans-retinoic acid (ATRA)
  for acute promyeloid leukemia (APL), 75
  induction of differentiation of undifferentiated, immortalized embryonal carcinoma cells, 71
androgen-dependent LAPC9 PCa xenograft tumors, 22
antiangiogenic therapies, 69
anti-CD44 activating antibody (H90), 98
Armstrong, Lance. *See* teratocarcinomas
asymmetric cell division. *See also* Notch cell signaling pathway; Wnt signaling pathway
  four steps of, 148
  Notch/Wnt signaling regulation of/regulation by, 139–140
  Numb protein distribution and, 36
  Par6 polarity protein and, 149–150
  self-renewal via, 36, 128
  and stem cell aging, 148–150
Asymmetric Enhancer (ASE)
Aurora kinase A (NF-kB activator), 57

basal cell carcinoma (BCC), 114
  cyclopamine, topical administration, 114
  HH/GLI signaling and, 117–118
basal-like carcinoma (breast cancer subtype), 50
basal-like phenotype
  of breast cancer stem cells, 51
  of (normal) mammary gland stem cells, 50
basic helix-loop-helix (bHLH) transcription repressors, of the hairy/enhancer-of-split-related (H/Espl) family, 141
Bc12 null mouse, hair graying (murine model) study, 33
BCR-ABL translocation, in chronic myeloid leukemia (CML), 95
Beard, C., 2
benign cells, transformation from benign cells, 70
benign prostatic hyperplasia (BPH), 21
β-catechin. *See also* Wnt/β-catechin cell signaling pathway
  activation of Notch signaling mediation, 36
  activation of Wnt1 signaling, 37
  E-Cadherin and, 55, 81
  hypoxia survival and, 59
  inhibition by Axin overexpression, 97
  interaction with HIF-1α, 57
  localization in β-catenin transgenic mice, 56
  mRNA expression
  prostate tumors and, 23
  targeting of CK5, CD44, Jagged-1, CA-IX, 55–56
BH3 mimetics, 100
Bhatt, R. I., 3
Bissell, M. J.
BMI-1 oncogene-driven pathway, 82
BMI-1 stem cell renewal factor, 40, 117
BMP receptor IA gene, 38–39
bone morphogenetic proteins (BMPs)
  and human ES cells
    ectodermal/mesodermal differentiation signal conferred by, 141

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-89628-3 - Cancer Stem Cells
Edited by William L. Farrar
Index
More information

bone morphogenetic proteins (*cont.*)
inhibition of embryonic ventricular zone progenitor cells, 142
promotion of hematopoietic specification, differentiation, and proliferation of, 142
interplay with Hedgehog, Notch, Wnt pathways, 146–148
maintenance of undifferentiated ES cells, through BMP Smads activation, 141
role in stem cell compartments of the colon, 144
tumor stroma-derived, 38, 80–81
Bonnet, D., 94
brain cancer, 3, 7
BRCA-I mutation carrier women, 50
breast cancer. *See also* SNAI2 gene expression
basal-like carcinoma subtype, 50
BMI-1 role in, 82
cancer stem cell–directed therapy for, 81
$CD44^+CD24^-$ cells, 8
CSCs identification, 2
ductal breast carcinoma xenografts, 51
EGFR upregulation as Her-2/neu (c-erb-B2), 81
HH/GLI-signaling and, 114
IL-6/SNAI2 upregulation, 56
mesenchymal breast tumors, 55
SP isolation from, 3, 8
Wnt-7b downregulation in, 81
breast cancer stem cells
ABCG2 (ATP ABC transporter) and, 77
basal-like phenotype of, 51
Notch-3 importance for survival of, 53–54
Wnt pathway as gene therapy target of, 81
5′-bromo-deoxyuridine (BrdU), 17
Brunschwig, A., 2

CA-IX 1 gene
β-catenin targeting of, 55–56
IL-6 upregulation of, 52–53
CA-IX. *See* carbonic anhydrase isoenzyme-IX (CA-IX)
cancer cells hierarchy
leukemia/$CD34^+CD38^-$ cells, 2, 5, 94–95
cancers. *See also* breast cancer; colon cancer; cutaneous melanoma; gastrointestinal cancer; Gorlin syndrome; leukemias; nasopharyngeal carcinoma; nonmelanoma skin cancers; ovarian cancer; pancreatic cancer; prostate cancer (PCa); teratocarcinomas; thyroid cancer
Bcl-xl upregulation in, 100
causes/mechanism of (hypotheses), ix, 1, 36, 109
cell lineages and, 69–71, 79
Hedgehog/GLI signal transduction and development of, 113–114
NF-κB activation, 99–100
reason for eradication failures, 40
reformation of therapy-resistant CSCs, 69
as a “stem cell disease,” 54.10
stem-cell-like nature of
cancer stem cell–directed therapy. *See also* Notch cell signaling pathway, as cancer therapeutic target
actions necessary for success, 69
breast cancer, 81
cancer stem cell signals, 80–81
developmental difficulties, 77
Hedgehog/GLI signaling and, 109, 118–120
Her-2/Neu, 81–82
inhibition of CST signaling pathways, 80
resistance to
stem cell phenotype association, 59
by tumor-initiating cells, x
“stemness” and outcome predictions, 77
targeting of Notch signaling, 132
Wnt, 81
cancer stem cells (CSCs) 16–18 . *See also* prostate cancer stem cells
cell lineages, 69–71
chemotherapy resistance of, 77, 129
differentiating agents,the environment and, 81
Hedgehog/GLI signaling in, 114–118
historical background, 2
hypothesis of
cancer stem cell hypothesis, 1–2, 17
“embryonal rest” hypothesis, 2
stochastic hypothesis, ix
identification of
cell surface markers, 4–5
culture of nonadherent spheres, 5–6
phenotypic assays, 17
side populations (SP), 3–4
inhibition of
delivery of iRNA, 83–85
inhibitory RNA, 83
molecular inhibitors, 85–86
oligonucleotides, 83
Notch signaling in, 128–129
“poised” lineage predicting genes in, 152–153
properties and characteristics of
clonogenicity *in vitro*, 16
self-renewal.*See* (self-renewal of cancer stem cells)
tumor heterogeneity, establishment of, 9
tumorigenicity, 6–7, 17
in vivo, 16
quiescent (dormant) cancer cells vs., 78–79
self-renewal/differentiation potential of, 129
carbonic anhydrase isoenzyme-IX (CA-IX), 49
Casein Kinase I (CKI), 111–112
CD20 melanoma marker, 34
CD33 expression in LSCs (from AML patients), 98
$CD34^+CD38^-$/$CD34^+CD38^+$ cells 2, 5 . *See also* hematopoietic stem cells (HSCs); leukemic stem cells
$CD44^+/\alpha2\beta1^{high}/CD133^+$ cells, 23
$CD44^+CD24^-$ cells (of breast cancer), 6, 8–9
CD44 expression in $CD34^+CD38^-$ cells (from AML), 98
CD44+ (hyaluronan receptor CD44) gene, 51
in breast cancer stem cells, 57

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-89628-3 - Cancer Stem Cells
Edited by William L. Farrar
Index
More information

CD44 glycoprotein (cell surface marker), 4
  β-catenin targeting of, 55–56
  expression, by human prostatic basal cells, 22–23
CD123 (IL-3 receptor alpha) phenotypic marker in LSCs, 97–98
$CD133^+/\alpha 2\beta 1^+$ cells, 20
$CD133^+$ cells, 5
CD133 neuroectodermal tumor marker. *See* Prominin-1 (CD133) cell surface marker
CD138 (cell surface marker), 5
cell lineages and cancer, 69–71, 79 . *See also* transit-amplifying cells
cell surface markers, 4–5
  CD20, 34
  $CD34^+CD38^-$, 2, 5, 101
  $CD44^+CD24^-$, 6
  CD44 glycoprotein, 4, 22–23, 55–56, 101
  CD96, 101
  CD123, 101
  CD138, 5
  CLL-1, 101
  drawbacks to usage, 5
  Prominin-1 (CD133), 4, 34–35, 40
  Sca-1 (Stem Cell Antigen-1), 20
  somatic SCs and, 18
cellular hierarchy, description, 15–16
central nervous system (CNS), sphere formation by CSCs, 5
c-Fos/c-Jun mediated transcription, 71
chemotherapy
  action on proliferating cancer transit-amplifying cells, 69
  with ATRLA treatment, for APL, 75
  CD44+/MS generating cells presence in breast cancer after, 58
  cisplatin-based cytoxic, for teratocarcinoma, 71
  cyclic, for AML, 77–78
  with FLT3, for pediatric AML patients, 76
  resistance of CSCs to, 129
chronic myeloid leukemia (CML), 73–74
  BCR-ABL translocation/chronic phase patients, 95
  CD44 mice studies, 98
  G-6-PD studies in patients with, 94
  imatinib, blocking effect in, 73–74
  Philadelphia chromosome in, 73, 94
  stages of maturation arrest, 72
cisplatin-based cytoxic chemotherapy, for teratocarcinoma, 71
CK5/6 expression (in mammary gland basal-like phenotype), 50
  β-catenin targeting of, 55–56
Clevers, H., 144
CLL-1/CD96 phenotypic markers, in LSCs (from AML patients), 98
clonal selection model of metastasis, 39–40
clonogenic in vitro cancer stem cells (CSCs), 16
colon cancer, 7
colony initiation in vitro, 2
comparative genomic hybridization (CGH), of melanoma stem cells, 35–36
Conheim, Julius, 2
CSCs. *See* cancer stem cells (CSCs)
Cunha, G. R., 20–21
cutaneous melanoma (defined), 31
CXCR4 (fusin) chemokine (CXC) receptor, for SFF-1 (CXCL12), 98
cyclopamine (SMOH antagonist), 114, 118
Cytokeratin 5/6 (CK5/6), overexpression of, 49

Decapentaplegic (Dpp), 149
Delta-like (D111, D113, D114) notch ligands, 129–130, 132
Denekamp, J., 78
dibutyryl-cAMP, with RA, 71
Dick, J. E., 94
Dickkopf (DKK) gene family, 145–146
differentiation theory
  of leukemia, 69, 73
  stemness and, 70–71
  of teratocarcinoma, 69, 71–72
dihydrotestosterone (DHT), conversion from testosterone, 18
DKK3. *See* Reduced Expression in Immortalized Cells (REIC)
DKK gene family. See Dickkopf (DKK) gene family
DNA analog labeling, 17
Dontu, G., 148
Drosophila
  β-spectrin phenotype, 143–144
  Elav protein, 146
  Lgl secretion of Decapentaplegic, 149
  musashi in nucleus of, 146
  Numb regulation of Notch signal pathway, 135, 149
  $Ttk69/p21^{Cip1}$ blocking by musashi, 147
drug resistance of stem cells, 77
ductal breast carcinoma xenografts, 51
ductal carcinoma in situ (DCIS)

E3 ubiquitin ligase. *See* Itch (E3 ubiquitin ligase)
EGFr expression (in mammary gland basal-like phenotype), 50
  MS survival association with, 54
  Notch-3 gene crosstalk with, 53–54
Elav orthologs (mammalian), 146
embryogenesis, 15
embryonal carcinoma, 71
"embryonal rest" hypothesis (Virchow), 2
embryonic stem cells (ESCs), 15 . *See also* human embryonic stem cells (hESCs)
  cell markers derived from, 4, 33
  differentiation/development of, 128
  lentiviral vectors and differentiation of, 84
  TGF-β family signaling in, 140–141
endothelium-associated genes, 39
ephrin receptor A2, endothelium-associated gene, 39

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-89628-3 - Cancer Stem Cells
Edited by William L. Farrar
Index
More information

epidermal growth factor receptor (EGFR), 49
  promotion of neural stem cells, 113
  upregulation as Her-2/neu in breast cancer, 81
epithelial tumors. *See* prostate cancer (PCa)
ERα expression. *See* Estrogen Receptor alpha (ERα) expression
Estrogen Receptor alpha (ERα) expression, 49–50
extracellular receptor kinase (ERK), 52–53

Fang, D., 35
Fialkow, P. J., 94
Fine, H. A.
5′-bromo-deoxyuridine (BrdU), 17
Flt3 (FMS-like tyrosine kinase), 99
FLT3. *See* FMS-like receptor tyrosine kinase 3
Fluorescence Activated Cell Sorter (FACS) analysis, 22, 35–36
FMS-like receptor tyrosine kinase 3 (FLT3), testing for AML, 76
frank leukemia, from leukemic stem cells, 96
Frizzled-5 (Wnt5a receptor), 38

G-6-PD studies. *See* glucose-6-phosphate dehydrogenase (G-6-PD) studies
gastrointestinal tissues and cancers, 81, 143–144
Gene Expression Omnibus (GEO), 100–101
Gli2-induced tumors, 118
glioblastoma multiforme, 116–117
glioblastoma stem cells, 34–35, 38
GLI zinc finger transcription factors, 110–111
glucose-6-phosphate dehydrogenase (G-6-PD) studies, 94
Glycogen Synthase Kinase 3 beta (GSK3β), 111–112
Goodell, M. A., 3
Gorlin syndrome, 114
Grichnik, J. M., 35
GSK3-beta inhibitors
  musashi induction of, 147
  phosphorylation role of, 111–112
  TDZD-8 vs., 100
  Wnt pathway activation by, 145
Gupta, P. B., 39

H90 (anti-CD44 activating antibody), 98
hair graying (murine model) studies, 33
Hedgehog cell signal transduction, 24, 37–38, 80–81
  interplay with Wnt, BMP, Notch pathways, 146–148
  Numb regulation of, 36
  regulation of leukemia stem cells (LSCs), 101
Hedgehog/GLI (HH/GLI) signal transduction. *See also* Gorlin syndrome; Patched (PTRCH); Resistance, Nodulation, Division (RND) family members; Smoothened (SMOH); Sonic-Hedgehog (SHH) pathway
  actions of GLI proteins, 111–113
  BMI-1 and, 117
  and cancer development, 113–114
  characteristics of, 110
  embryonic development/adult organism tasks, 110
  glioblastoma multiforme and, 116–117
  GLI zinc finger transcription factors, 110–111
  Gorlin syndrome and, 114
  implication in stem/cancer cell activation, 115
  influence of intraflagellar transport proteins (IFT) on, 110–111
  inhibition of, in cancer therapy, 118–120
  interactive pathways of, 120
  medulloblastoma and, 115–116
  multiple myeloma (MM) and, 117
  in stem and cancer stem cells, 114–118
  stimulating function of hair follicle stem cells, 115
  synergistic actions of, 115
hematopoietic stem cells (HSCs)
  $CD34^+/CD38^-$ subpopulation, 94–95
  maintenance by Wnt function, 145
  role of, 93
  shared markers ($CD34^+/CD38^-$) with LSCs, 96
  TGF-β family members in, 142–143
hepatocellular carcinoma, 3, 8, 144
Her-2/Neu, and cancer stem cell–directed therapy, 81–82
hESCs. *See* human embryonic stem cells (hESCs)
hierarchy of cancer cells
  PCa lineage, 23
HIF-1α gene
  NF-kB triggering of, 57
  Stat-3 upregulation activation of, 57
hTERT immortalized HPCa-derived epithelial cell lines, 23
^{3}H-thymidine/5′-bromo-deoxyuridine, 17

identification of cancer stem cells
  cell surface markers (*See* cell surface markers)
  culture of nonadherent spheres, 5–6
  side populations (SP), 3–4
IFT. *See* intraflagellar transport proteins (IFT)
IL-6 (interleukin-6), 49, 51–55
  MS expression of, 52
  Notch-3 interplay with, 54–55
  promotion of xenograft tumors, 52, 57
  upregulation in breast cancer, 56–57
imatinib, blocking effect in CML, 73–74
immunofluorescence-based cell sorting
  of ABCB5 cells, 41
  for ABCG2 MDR transporter, 22
  for CD44+ cells (from xenograft tumors), 22
  for CD133/ABCB5/2% of G3361 melanoma cells, 41
  of CD133 cells (from melanoma cells), 35, 41
  hESCs expression of Cripto-1
inhibition of cancer stem cells (CSCs)
  delivery of iRNA, 83–85
  inhibitory RNA, 83
  molecular inhibitors, 85–86
  oligonucleotides, 83

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-89628-3 - Cancer Stem Cells
Edited by William L. Farrar
Index
More information

inhibitory RNA (iRNA), 83–85
intraflagellar transport proteins (IFT), influence on HH/GLI signaling, 110–111
Itch (E3 ubiquitin ligase), 134–135

Jagged-1 gene, 49
  β-catenin targeting of, 55–56
  IL-6 upregulation of, 52–53
  overexpression in LSCs from AML patients, 101
Jagged-2 gene
Janus family kinase (JFK), 80–81

karyotyping, of melanoma stem cells, 35–36
keratinocyte (hair root/sheath) progenitor cells, 38–39
Kern, S. E., 79
Kit melanocyte developmental marker, 32
Kobielak, K., 38

LAPC9 PCa (androgen dependent) xenograft tumors, 22
Lapidot, T., 94
Lef1 melanocyte developmental marker, 32
leukemias. *See also* acute myeloid leukemia (AML); acute promyeloid leukemia (APL); chronic myeloid leukemia (CML); promyelocytic leukemia (PML)
  CSCs identification, x, 2
  described, 72–73
  differentiation therapy of, 69, 73
  mTOR necessity for survival, 99
  regrowth of, 76–77
  SP isolation from, 3
leukemia stem cells (LSCs). *See also* acute myeloid leukemia (AML)
  activated survival pathways, 97
  cell of origin models, 95–96
  cellular/molecular analysis of, 96–97
  clinical implications
    diagnostic approach considerations, 101–102
    remission bone marrow evaluation, 102–103
  frank leukemia from, 96
  identical twin studies, 96
  identification of, in human leukemias, 94
  Notch/Hedgehog/Wnt signaling pathway regulation of, 101
  shared markers ($CD34^+/CD38^-$) with HSCs, 96
  therapeutic response of, 77–78
leukemia stem cells (LSCs), therapy
  molecular targets
    Flt3 (FMS-like tyrosine kinase), 99
    NF-κB transcription factor, 99–100
    PI3K (phosphatidyl-inositol 3 kinase), 99
  other approaches
    BH3 mimetics, 100
    in silico screening in GEO, 100–101
    TDZD-8, 100
  phenotypic markers
    CD33 expression, 98
    CD44 expression, 98
    CD123 (IL-3 receptor alpha), 97–98
    CLL-1/CD96, 98
    CXCR4 (fusin), 98
leukemic blast cells, 96
lobuloalveolar hyperplasia, 81
loco-regional disease, cure rate, 31
long-term label-retaining cells (LRCs), 17
lung cancer
  HH/GLI-signaling and, 114, 117
  self-renewal assays from isolated CSCs, 8
  SP isolation from, 3
lymphovascular tumor emboli, 56

malignant cells, transformation to benign, 70
mammary gland stem cells (normal), 50
  inflammatory/hypoxic profile in regulation of, 56–58
    chemoresistance as consequence, 58–60
  Wnt/β-catenin cell activation and, 145
mammospheres (MS)
  BRCA-I gene vitro knockdown and, 50
  breast CSC phenotype regulation in, 51
  defined, 49–50
  from ductal breast carcinoma (characteristics), 51, 54
  EGFr and survival of, 54
  IL-6/gp130 expressed by, 52
  increased Notch-3 gene expression, 148
  invasive capability promoted by SNAI2 gene expression, 56
  SNAI2 gene expression in, 50, 55–56
medulloblastoma, 34–35, 114
  CD133 expression in, 34–35
  HH/GLI signal transduction and, 115–116
MEK/Extracellular Signal-Regulated Kinase (ERK) pathway, 112
melanocytes. *See also* vitiligo (depigmentation disorder)
  developmental markers, 32–33
  hair graying (murine model) studies, 33
  skin/hair, physiological maintenance of, 32–33
melanocyte stem cell, adult, 32–33
  Dct-lacZ transgenic mice studies, 32
melanomas
  CD20 marker, 34
  CD133 expression, 35
  detection of BMI-1 expression in, 40
  origination (hypothesis) of, 31–32
  phenotypic heterogeneity in vitro and in vivo, 33–34
  survival regulation by SHH-GLI signaling, 37
  "vascular mimicry" by, 140
melanoma stem cells
  CD20 marker, 34
  CD133 marker, 4, 34–35, 40 . *See also* (Prominin-1 cell surface marker)
  Dct-lacZ transgenic mice studies, 32
  developmental gene expression, 34
  dormant, role in metastasis/therapeutic resistance of melanoma stem cells, 39–41

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-89628-3 - Cancer Stem Cells
Edited by William L. Farrar
Index
More information

melanoma stem cells (*cont.*)
  embryonic stem cell markers, 33
  FACS analysis, for identification, 35–36
  hair graying mouse models, 33
  karyotyping/CGH, 35–36
  niche of, 38–39
  Nodal knockdown cell differentiation, 39
  self-renewal/transdifferentiation properties, 33–36
  spheroid cells, 34
  stemness/metastatic capacity of, 40
mesenchymal breast tumors, 55
metastasis
  clonal selection model, 39–40
  defined, 39
  Slug requirement for, 40
  stemness/melanoma cell correlation study, 40
mice models
  BRCA-I mutation defective, 50
  CD44 studies of CML, 98
  HH/GLI signal transduction and, 37, 114
  of leukemia, 96
  $Mitf^{vit}$ mice, hair graying study, 33
  SCID mice, and human leukemic cells, 79
  transgenic, Dct-lacZ, melanocyte stem cell studies, 32
Mitf melanocyte developmental marker, 32
$Mitf^{vit}$ mice, hair graying (murine model) study, 33
molecular inhibitors, for stem cell signaling pathways, 85–86
molecular signal pathways for maintaining stemness
  Hedgehog signaling, 24, 37–38, 80–81
  Notch signaling, 24, 36–37
  Wnt signaling, 24, 37–38
molecular targets in leukemia stem cells
  Flt3 (FMS-like tyrosine kinase), 99
  NF-κB transcription factor, 99–100
  PI3K (phosphatidyl-inositol 3 kinase), 99
Monzani, E., 35, 40
Moriyama, M., 37
MS. *See* mammospheres (MS)
mTOR (mammalian target of rapamycin), and LSCs survival, 99
multiple myeloma (MM), 117
Musashi (Msi1)
  blocking translation of *Drosophila* $Ttk69/p21^{Cip1}$, 147
  global role in cell fate determination, 146
  interference with pre-mRNA splicing, processing, nuclear-cytoplasmic transport, 146
  -mediated reduction of DKK3 increased B-catenin stability, 145
  and notch cell signaling pathway, 146–148
  in nucleus of *Drosophila* cells, 146

Nanog embryonic stem cell marker, 33
nasopharyngeal carcinoma, SP isolation from, 3
Nestin stem cell marker, 34–35, 40
neural crest stem cells, 18, 32, 34
  Slug regulation of, 39–40
neural stem cells, 38, 115
  EGF/Sonic HH promotion of, 113
  HH/GLI persistent activation of, 116
  TGF-β family members in, 142
neuroectodermal tumors, 34–35
NF-κB transcription factor, 57, 99–100
NICD. *See* Notch Intracellular cytoplasmic domain (NICD)
niches
  epithelial adult SCs, 32
  melanoma SCs, 38–39
  somatic SCs, 16
Nishimura, E. K., 33, 37
Nodal embryonic factor, knockdown breast carcinoma cell/melanoma cell differentiation, 39
Nodal knockdown melanoma cell differentiation, 39
NOD/SCID (non-obese diabetic/severe combined immunodeficiency) mouse model
  androgen-dependent LAPC9 PCa xenograft tumors, 22
  $CD34^{+}/CD38^{-}$ implantation into, 94
  CD133 cells, injection into, 35
  tumor formation by CD44+CD24–cells in, 8
non-Hodgkin's lymphoma, 34
nonmelanoma skin cancers, 37, 114, 118
Notch-3 gene, 49, 80–81
  EGFr pathway crosstalk with, 53–54
  IL-6 interplay with, 54–55
  IL-6 upregulation of, 52–53
  increased expression in mammospheres, 148
  regulation of leukemia stem cells (LSCs), 101
  Stat-3 targeting of, 53
Notch cell signaling pathway. *See also* basic helix-loop-helix (bHLH) transcription repressors, of the hairy/enhancer-of-split-related (H/Espl) family; Delta-like (D111, D113, D114) notch ligands; Jagged-1 gene; Jagged-2 gene
  asymmetric cell division and, 36, 128–132
  described, 129–132
  functional interactions with TGF-β/Smad, 141
  global role in cell fate determination, 146
  implication in stem/cancer cell activation, 115
  interplay with BMP, Hedgehog, Wnt pathways, 146–148
  ligand identification, 129–130
  musashi and, 146–148
  Numb regulation of, 36
  role in tumorigenesis, 24
  transmembrane receptor activation, 129
Notch cell signaling pathway, as cancer therapeutic target, 132
  blockade receptor/ligand interaction
    anti-Notch antibody, 134
    neutralizing anti-D114 antibodies, 134

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-89628-3 - Cancer Stem Cells
Edited by William L. Farrar
Index
More information

neutralizing DLL ligands, 134
recombinant Notch extracellular domain protein, 133
blocking proteolytic cleavage events
S1 cleavage blockade, 132–133
S2 cleavage blockade, 133
S3 cleavage blockade, 133
NICD inhibition/dominant negative-MAML1, 135
suppressing Notch protein expression
RNAi vs. Notch signaling components, 135
ubiquitination controls, 134. (*See also* Itch; Se110)
Notch Intracellular cytoplasmic domain (NICD), 130, 135
Nuclear Factor-kappaB (NF-kB)-dependent mechanism, 56
role in mammary gland morphogenesis, 56–57
triggering of HIF-1α gene expression, 57
Numb gene product, 36, 135
promotion of ubiquitination/proteasomal Notch degradation, 146

Oct4 embryonic stem cell marker, 33, 80–81
oligonucleotides, 83
ovarian cancer, SP isolation from, 3

pancreatic cancer, 7
HH/GLI-signaling and, 114
Par6 polarity protein, and asymmetric cell division, 149–150
Patched (PTRCH), HH ligand receptor, 110 . *See also* Gorlin syndrome
Patrawala, L., 3, 7
Pax3 melanocyte developmental marker, 32, 34
PCa. *See* prostate cancer (PCa)
phenotypic markers in leukemia stem cells
CD33 expression, 98
CD44 expression, 98
CD123 (IL-3 receptor alpha), 97–98
CLL-1/CD96, 98
CXCR4 (fusin), 98
Philadelphia chromosome (in CML), 73, 94
phosphinositide-3 kinase (PI3K)/AKT pathway, 112
PI3K (phosphatidyl-inositol 3 kinase) lipid kinase, 99
Pierce, G. B., 70
"poised" lineage predicting genes in CSCs, 152–153
Polycomb group ring finger gene family, 40
PRAJA (TGF-β/BMP-regulated protein), 144
progenitor cells. *See* prostatic/prostatic stem/progenitor cells
Prominin-1 (CD133) cell surface marker, 4, 34–35, 40
promyelocytic leukemia (PML), 74
prostate cancer (PCa), 7 . *See also* benign prostatic hyperplasia (BPH); prostatic intraepithelial neoplasia (PIN)
BMI-1 role in, 82
cell of origin of, 25
description, 21
etiology of, 21
genetic mutations/epigenetic alterations and, 24
HH/GLI-signaling and, 114, 117
hTERT immortalized HPCa-derived epithelial cell lines, 23
human lineage hierarchy, 23
PTEN cell signaling pathway and, 24–25
self-renewal assays from isolated CSCs, 8
SP isolation from, 3
xenograft tumors (androgen-dependent LAPC9), 22–23
prostate cancer stem cells, 21–23
prostate gland
androgen deprivation/restoration, 18
architecture of, 18
basal vs. luminal cell discrimination, 19–20
$CD133^{+}/\alpha 2\beta 1^{+}$ cells, 20
description, 18
identification/localization of SCs, 19–20
signaling networks, 18
prostatic intraepithelial neoplasia (PIN), 21
prostatic/prostatic stem/progenitor cells, 18–21
Protein Kinase A (PKA), 111–112
Protein Kinase C δ pathway, 112
PTEN cell signaling pathway, 24–25
pulse labeling studies (Pierce & Wallace), 70

radiation and drug resistance, of stem cells, 77
radiation/drug resistance of stem cells, 77
CSCs vs. quiescent (dormant) cancer cells, 78–79
leukemic stem cells, therapeutic response, 77–78
Radtke, F., 144
rapamycin, 99
Reduced Expression in Immortalized Cells (REIC), 145
Resistance, Nodulation, Division (RND) family members, 110–112
retinoic acid (RA)
for acute promyeloid leukemia, 74–75
importance in embryogenesis, 151
for teratocarcinoma, 71–72
Reynolds, B. A., 5
rhabdomyosarcoma, 114
Ricci-Vitiani, L., 8
RNA interference (RNAi)
inhibition of normal cells, 80
vs. Notch signaling components, 135

Sca-1 (Stem Cell Antigen-1), 20
Se110 (F-box/WD40 repeat-containing protein), 135
self-renewal
of cancer stem cells (CSCs), 7–8
of bona fide CSCs, 17–18

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-89628-3 - Cancer Stem Cells
Edited by William L. Farrar
Index
More information

self-renewal (*cont.*)
and CSC cell-fate molecular mechanisms, 23–25
serial transplantation, 8
in vitro renewal, 8
of melanoma stem cells, 33–36
serial transplantation of CSCs, 8
SHH-GLI signaling, 37
SHH pathway. *See* Sonic-Hedgehog (SHH) pathway
Shibata, D., 79
side population (SP) phenotype of CSCs
described, 3–4
for discrimination of SCs, 17
Hoechst 33352 identification of, 35–36, 58, 103
melanoma stem cells and, 40
sorting of, 6, 77
skin cancers, nonmelanoma, 37, 114, 118
Slug, regulation of neural crest SCs, 39–40
Smad
activation of transcription factors, 140
cooperation with Wnt signaling, 141
crosstalk of TGF-β family signaling through, 140
Smoothened (SMOH), 110–112
antagonists of, 118
glioma cancer stem cells, HH/GLI and, 117
HH activation/hair growth induction, 115
SNAI2 gene expression (in basal/stem cell–cells), 49–52, 55–56
mechanism of action, 55
MS invasive capability promotion by, 56
overexpression in lymphovascular tumor emboli, 56
upregulation in breast cancer, 56–57
soft agar colonies (over generations), 8
somatic stem cells
functions of, 16
mutated, fused with normal SCs, 36
quiescence property, 17
Sonic-Hedgehog (SHH) pathway, 22, 80–81
promotion of neural stem cells, 113
role in tumorigenesis, 24, 116
Southam, C. M., 2
Sox10 melanoma developmental gene expression, 34
spheres/spheroids (nonadherent), 5–6, 8, 17
of luminal breast cancer cells, 51
multicellular, from normal mammary glands (*See* mammospheres (MS))
propagation, in metastatic melanoma, 34
squamous cell carcinoma, 70
Stat-3
HIF-1α gene upregulation triggered by, 57
Notch-3 gene targeting by, 53
Stecca, B., 37
stem cells (SCs). *See also* cancer stem cells (CSCs); embryonic stem cells (ESCs); melanocyte stem cell, adult; prostatic/prostatic stem/progenitor cells; somatic stem cells
asymmetric division, 16
medulloblastoma origination from, 115–116
molecular signal pathways for maintaining stemness
Hedgehog signaling, 24, 37–38, 80–81
Notch signaling, 24, 36–38
Wnt signaling, 24, 37–38
neural crest derivation, 34
primitive, undifferentiated, 15
radiation/drug resistance of, 77
"self-renewal" feature, 16 (*See also* self-renewal of CSCs)
somatic stem cells, 16
stemness (state of a cell)
differentiation theory and, 70–71
gene expression signatures associated with, 82
leukemic cell differentiation and, 69
of melanoma stem cells, 34, 40, 42
molecular signal pathways for maintaining
Hedgehog signaling, 24, 37–38, 80–81
Notch signaling, 24, 36–37
Wnt signaling, 24, 37–38
stochastic hypothesis of CSCs, ix
stromal-epithelial cell signaling, 20–21

TACE. See Tumor Necrosis Factor Alpha Converting Enzyme (TACE)
TDZD-8, (4-Benzyl-2-methyl-1, 2, 4-thiadiazolidine-3, 5-dione), for LST therapy, 100
TEL-AML chromosomal translocation, 96
Teratocarcinoma Derived Growth Factor (TDGF). *See* Cripto-1 epidermal growth factor
teratocarcinomas
described, 71
irradiation/cisplatin-based cytoxic chemotherapy, 71
retinoic acid/differentiation therapy of, 69, 71–72
surgical treatment, 71
testosterone, conversion to DHT, 18
TGF-β superfamily. See Transforming Growth Factor-beta (TGF-β) superfamily
^{3}H-thymidine/5'-bromo-deoxyuridine, 17
thyroid cancer, SP isolation from, 3
tissue recombination techniques, 20–21
Topczewska, J. M., 39
transdifferentiation properties, of melanoma stem cells, 33–36
Transforming Growth Factor-beta (TGF-β)/SMAD pathway, 112
Transforming Growth Factor-beta (TGF-β) superfamily, 39 . *See also* activins; bone morphogenetic proteins; Decapentaplegic (Dpp); Lefty (embryonic stem-cell derived factor) molecules; Nodal embryonic factor
description, 140
functional interactions with Notch signaling, 141
in gastrointestinal tissues/cancers, 143–144

© in this web service Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
978-0-521-89628-3 - Cancer Stem Cells
Edited by William L. Farrar
Index
More information

in hematopoietic stem cells, 142–143
mediation of germ layer differentiation, 141
in neural stem cells, 142
signaling in embryonic stem cells, 140–141
transgenic mice
Dct-lacZ, melanocyte stem cell studies, 32
increased Sca-1/CK6+ stem/progenitor cells, and side populations, 145
transit amplifying cells, 69–70
Trott, K. R., 78
tumorigenicity of CSCs, 6–7, 17
cell signaling pathways, 24, 118 (*See also* individual pathways)
Hedgehog/GLI signal transduction and, 114
prostate cancer (PCa), 23
Tumor Necrosis Factor Alpha Converting Enzyme (TACE), 56, 130, 133
tumor stroma-derived bone morphogenetic proteins (BMPs), 38
21-kDa guanine-nucleotide binding protein mutation, in AML, 76
Tyr melanocyte developmental marker, 32
tyrosine-kinase receptor 1, endothelium-associated gene, 39

ubiquitin activating enzyme-E1 like protein (UBE1L), 75

vascular endothelial cadherin (VE-Cadherin) gene, 39
"vascular mimicry" by melanomas, 140
Vimentin gene (mesenchymal hallmark), 49
co-expression in breast cancer, melanoma
presence in mammospheres, 55
role of, 51–52
Virchow, Rudolph, 2
Vitamins A and D, anti-cancer properties/ differentiation promoting effects, 151–152
vitiligo (depigmentation disorder), 33

Wallace, C., 70
Wnt/β-catechin cell signaling pathway, 24, 37–38, 80–81
activation in mammary gland, 145
cancer stem cell–directed therapy and, 81
Wnt signaling pathway, 37–38
asymmetric cell division and, 36, 128, 139–140
Dickkopf (DKK) gene family inhibition of, 145–146
GSK3-inhibitor activation of, 145
implication in stem/cancer cell activation, 115
interplay with Wnt, Hedgehog, BMP, Notch pathways, 146–148
maintenance of hematopoietic stem cells, 145
regulation of leukemia stem cells (LSCs), 101
regulation of/regulated by asymmetric cell division, 36, 128, 139–140
role of, 144–145
Smad cooperation with, 141

xenograft tumors
androgen-dependent LAPC9 PCa, 22–23
ductal breast carcinoma, 51
HH/GLI signal transduction and, 37, 114
IL-6 promotion, 52, 57
NOD/SCID mouse model, 103

© in this web service Cambridge University Press www.cambridge.org