

# Chapter 86

## Biology of Hair Follicles

George Cotsarelis &

Vladimir Botchkarev

### REFERENCES

1. Cotsarelis G, Millar SE: Towards a molecular understanding of hair loss and its treatment. *Trends Mol Med* **7**:293, 2001 [PMID: 11425637]
2. Stenn KS, Cotsarelis G: Bioengineering the hair follicle: Fringe benefits of stem cell technology. *Curr Opin Biotechnol* **16**:493, 2005 [PMID: 16098737]
3. Hebert JM et al: FGF5 as a regulator of the hair growth cycle: Evidence from targeted and spontaneous mutations. *Cell* **78**:1017, 1994 [PMID: 7923352]
4. Luetke NC et al: TGF alpha deficiency results in hair follicle and eye abnormalities in targeted and waved-1 mice. *Cell* **73**:263, 1993 [PMID: 8477445]
5. Mann GB et al: Mice with a null mutation of the TGF alpha gene have abnormal skin architecture, wavy hair, and curly whiskers and often develop corneal inflammation. *Cell* **73**:249, 1993 [PMID: 8477444]
6. Godwin AR, Capecchi MR: Hoxc13 mutant mice lack external hair. *Genes Dev* **12**:11, 1998 [PMID: 9420327]
7. van Genderen C et al: Development of several organs that require inductive epithelial-mesenchymal interactions is impaired in LEF-1-deficient mice. *Genes Dev* **8**:2691, 1994
8. Reddy S et al: Characterization of Wnt gene expression in developing and postnatal hair follicles and identification of Wnt5a as a target of Sonic hedgehog in hair follicle morphogenesis. *Mech Dev* **107**:69, 2001 [PMID: 11520664]
9. Sato N, Leopold PL, Crystal RG: Induction of the hair growth phase in postnatal mice by localized transient expression of Sonic hedgehog [see comments]. *J Clin Invest* **104**:855, 1999 [PMID: 10510326]
10. Botchkarev VA et al: Noggin is required for induction of hair follicle growth phase in postnatal skin. *FASEB J* **15**:2205, 2001 [PMID: 11641247]
11. Cotsarelis G: Epithelial stem cells: A folliculocentric view. *J Invest Dermatol* **126**:1459, 2006 [PMID: 16778814]
12. Stenn KS, Paus R: Controls of hair follicle cycling. *Physiol Rev* **81**:449, 2001 [PMID: 11152763]
13. Botchkarev VA et al: Neurotrophins in skin biology and pathology. *J Invest Dermatol* **126**:1719, 2006 [PMID: 16845411]
14. Botchkarev VA, Paus R: Molecular biology of hair morphogenesis: Development and cycling. *J Exp Zool* **298**:164, 2003 [PMID: 12949776]
15. Millar SE: Molecular mechanisms regulating hair follicle development. *J Invest Dermatol* **118**:216, 2002 [PMID: 11841536]
16. Schmidt-Ullrich R, Paus R: Molecular principles of hair follicle induction and morphogenesis. *Bioessays* **27**:247, 2004
17. Millar SE: The role of patterning genes in epidermal differentiation. In: *Cytoskeletal-Membrane Interactions and Signal Transduction*, edited by P Cowin, M Klymkowsky. Austin, Landes Bioscience, 1997, p. 87
18. Chuong CM: *Molecular Biology of Skin Appendage Morphogenesis*. Austin, Landes Bioscience, 1998
19. Oro AE, Scott MP: Splitting hairs: Dissecting roles of signaling systems in epidermal development. *Cell* **95**:575, 1998 [PMID: 9845357]
20. Schwartz J: 'Sonic hedgehog' sounded funny at first. *New York Times* [Nov 12, 2006]; Week in Review, <http://www.nytimes.com/2006/11/12/weekinreview/12schwartz.html?ex=1183867200&en=77883ab62c250c8f&ei=5070>
21. Krumlauf R: Hox genes in vertebrate development. *Cell* **7**:191, 1994
22. Chuong CM et al: Gradients of homeoproteins in developing feather buds. *Development* **110**:1021, 1990 [PMID: 2100252]
23. Loomis CA et al: The mouse Engrailed-1 gene and ventral limb patterning. *Nature* **382**:360, 1996 [PMID: 8684466]
24. Cadieu E et al: Coat variation in the domestic dog is governed by variants in three genes. *Science* **326**:150, 2009. Epub 2009 [PMID: 19713490]

25. Mou C et al: Enhanced ectodysplasin-A receptor (EDAR) signaling alters multiple fiber characteristics to produce the East Asian hair form. *Hum Mutat* **29**:1405, 2008. [PMID: 18561327]
26. Levy V et al: Distinct stem cell populations regenerate the follicle and interfollicular epidermis. *Dev Cell* **9**:855, 2005 [PMID: 16326396]
27. Jamora C et al: Links between signal transduction, transcription and adhesion in epithelial bud development. *Nature* **422**:317, 2003 [PMID: 12646922]
28. Nanba D et al: Remodeling of desmosomal and hemidesmosomal adhesion systems during early morphogenesis of mouse pelage hair follicles. *J Invest Dermatol* **114**:171, 2000 [PMID: 10620134]
29. Rhee H, Polak L, Fuchs E: Lhx2 maintains stem cell character in hair follicles. *Science* **312**:1946, 2006 [PMID: 16809539]
30. Hardy MH: The secret life of the hair follicle. *Trends Genet* **8**:55, 1992 [PMID: 1566372]
31. Stark J, Andl T, Millar SE: Hairy math: Insights into hair-follicle spacing and orientation. *Cell* **128**:17, 2007 [PMID:17218249]
32. Gat U et al: De novo hair follicle morphogenesis and hair tumors in mice expressing a truncated beta-catenin in skin. *Cell* **95**:605, 1998 [PMID: 9845363]
33. Chan EF et al: A common human skin tumour is caused by activating mutations in beta-catenin. *Nat Genet* **21**:410, 1999 [PMID: 10192393]
34. Mikkola ML, Thesleff I: Ectodysplasin signaling in development. *Cytokine Growth Factor Rev* **14**:211, 2003 [PMID: 12787560]
35. Kere J et al: X-linked anhidrotic (hypohidrotic) ectodermal dysplasia is caused by mutation in a novel transmembrane protein [see comments]. *Nat Genet* **13**:409, 1996 [PMID: 8696334]
36. Headon DJ, Overbeek PA: Involvement of a novel Tnf receptor homologue in hair follicle induction [see comments]. *Nat Genet* **22**:370, 1999 [PMID: 10431242]
37. Mustonen T et al: Ectodysplasin A1 promotes placodal cell fate during early morphogenesis of ectodermal appendages. *Development* **131**:4907, 2004 [PMID: 15371307]
38. Zhang M et al: Ectodysplasin regulates pattern formation in the mammalian hair coat. *Genesis* **37**:30, 2003 [PMID: 14502575]
39. Noramly S, Morgan BA: BMPs mediate lateral inhibition at successive stages in feather tract development. *Development* **125**:3775, 1998 [PMID: 9729486]
40. Jung HS et al: Local inhibitory action of BMPs and their relationships with activators in feather formation: Implications for periodic patterning. *Dev Biol* **196**:11, 1998 [PMID: 9527877]
41. Jiang TX et al: Self-organization of periodic patterns by dissociated feather mesenchymal cells and the regulation of size, number and spacing of primordia. *Development* **126**:4997, 1999 [PMID: 10529418]
42. Patel K, Makarenkova H, Jung HS: The role of long range, local and direct signalling molecules during chick feather bud development involving the BMPs, follistatin and the Eph receptor tyrosine kinase Eph-A4. *Mech Dev* **86**:51, 1999 [PMID: 10446265]
43. Botchkarev VA et al: Noggin is a mesenchymally derived stimulator of hair-follicle induction. *Nat Cell Biol* **1**:158, 1999 [PMID: 10559902]
44. Viallet JP et al: Chick Delta-1 gene expression and the formation of the feather primordia. *Mech Dev* **72**:159, 1998 [PMID: 9533960]
45. Crowe R et al: A new role for Notch and Delta in cell fate decisions: Patterning the feather array. *Development* **125**:767, 1998 [PMID: 9435296]
46. Powell BC et al: The Notch signalling pathway in hair growth. *Mech Dev* **78**:189, 1998 [PMID: 9858728]
47. Crowe R, Niswander L: Disruption of scale development by Delta-1 misexpression. *Dev Biol* **195**:70, 1998 [PMID: 9520325]
48. Iseki S et al: Sonic hedgehog is expressed in epithelial cells during development of whisker, hair, and tooth. *Biochem Biophys Res Commun* **218**:688, 1996 [PMID: 8579575]
49. Bitgood MJ, McMahon AP: Hedgehog and Bmp genes are coexpressed at many diverse sites of cell-cell interaction in the mouse embryo. *Dev Biol* **172**:126, 1995 [PMID: 7589793]
50. St-Jacques B et al: Sonic hedgehog signaling is essential for hair development. *Curr Biol* **8**:1058, 1998 [PMID: 9768360]
51. Chiang C et al: Essential role for Sonic hedgehog during hair follicle morphogenesis. *Dev Biol* **205**:1, 1999 [PMID: 9882493]
52. Karlsson L, Bondjers C, Betsholtz C: Roles for PDGF-A and sonic hedgehog in development of mesenchymal components of the hair follicle. *Development* **126**:2611, 1999 [PMID: 10331973]
53. Platt KA, Michaud J, Joyner AL: Expression of the mouse Gli and Ptc genes is adjacent to embryonic sources of hedgehog signals suggesting a conservation of pathways between flies and mice. *Mech Dev* **62**:121, 1997 [PMID: 9152005]

54. Kaufman CK et al: GATA-3: An unexpected regulator of cell lineage determination in skin. *Genes Dev* **17**:2108, 2003 [PMID: 12923059]
55. Kopan R, Weintraub H: Mouse notch: Expression in hair follicles correlates with cell fate determination. *J Cell Biol* **121**:631, 1993 [PMID: 8486742]
56. Struhl G, Adachi A: Nuclear access and action of notch in vivo. *Cell* **93**:649, 1998 [PMID: 9604939]
57. Millar SE et al: WNT signaling in the control of hair growth and structure. *Dev Biol* **207**:133, 1999 [PMID: 10049570]
58. Kratochwil K et al: Lef1 expression is activated by BMP-4 and regulates inductive tissue interactions in tooth and hair development. *Genes Dev* **10**:1382, 1996 [PMID: 8647435]
59. Zhou P et al: Lymphoid enhancer factor 1 directs hair follicle patterning and epithelial cell fate. *Genes Dev* **9**:700, 1995 [PMID: 7537238]
60. Dunn S et al: Regulation of a hair follicle keratin intermediate filament gene promoter. *J Cell Sci* **111**:3487, 1998 [PMID: 9811563]
61. Andl T et al: Epithelial Bmpr1a regulates differentiation and proliferation in postnatal hair follicles and is essential for tooth development. *Development* **131**:2257, 2004 [PMID: 15102710]
62. Kobiela K et al: Defining BMP functions in the hair follicle by conditional ablation of BMP receptor IA. *J Cell Biol* **163**:609, 2003 [PMID: 14610062]
63. Yuhki M et al: BMPR1A signaling is necessary for hair follicle cycling and hair shaft differentiation in mice. *Development* **131**:1825, 2004 [PMID: 15084466]
64. Nehls M et al: New member of the winged-helix protein family disrupted in mouse and rat nude mutations. *Nature* **372**:103, 1994 [PMID: 7969402]
65. Segre JA et al: Positional cloning of the nude locus: Genetic, physical, and transcription maps of the region and mutations in the mouse and rat. *Genomics* **28**:549, 1995 [PMID: 7490093]
66. Brissette JL et al: The product of the mouse nude locus, Whn, regulates the balance between epithelial cell growth and differentiation. *Genes Dev* **10**:2212, 1996 [PMID: 8804315]
67. Meier N, Dear TN, Boehm T: Whn and mHa3 are components of the genetic hierarchy controlling hair follicle differentiation. *Mech Dev* **89**:215, 1999 [PMID: 10559501]
68. Frank J et al: Exposing the human nude phenotype [letter]. *Nature* **398**:473, 1999 [PMID: 10206641]
69. Whiting DA: Possible mechanisms of miniaturization during androgenetic alopecia or pattern hair loss. *J Am Acad Dermatol* **45**:S81, 2001
70. Murillas R et al: Expression of a dominant negative mutant of epidermal growth factor receptor in the epidermis of transgenic mice elicits striking alterations in hair follicle development and skin structure. *EMBO J* **14**:5216, 1995 [PMID: 7489711]
71. Schlake T: Segmental Igfbp5 expression is specifically associated with the bent structure of zigzag hairs. *Mech Dev* **122**:988, 2005 [PMID: 16024235]
72. Langbein L et al: K25 (k25irs1), K26 (k25irs2), k27 (k25irs3), and k28 (k25irs4) represent the type I inner root sheath keratins of the human hair follicle. *J Invest Dermatol* **126**:2377, 2006 [PMID: 16874310]
73. Langbein L, Schweizer J: Keratins of the human hair follicle. *Int Rev Cytol* **243**:1, 2005 [PMID: 15797458]
74. Wu H, Stanley JR, Cotsarelis G: Desmoglein isotype expression in the hair follicle and its cysts correlates with type of keratinization and degree of differentiation. *J Invest Dermatol* **120**:1052, 2003 [PMID: 12787134]
75. Gu LH, Coulombe P: Keratin expression provides novel insights into the morphogenesis and function of the companion layer in hair follicles. *J Invest Dermatol* **127**(5):1061, 2006 [Epub ahead of print]
76. Langbein L et al: A novel epithelial keratin, hK6irs1, is expressed differentially in all layers of the inner root sheath, including specialized Huxley cells (Flugelzellen) of the human hair follicle. *J Invest Dermatol* **118**:789, 2002 [PMID: 11982755]
77. Jave-Suarez LF et al: Androgen regulation of the human hair follicle: The type I hair keratin hHa7 is a direct target gene in trichocytes. *J Invest Dermatol* **122**:555, 2004 [PMID: 15086535]
78. Jahoda CA, Horne KA, Oliver RF: Induction of hair growth by implantation of cultured dermal papilla cells. *Nature* **311**:560, 1984 [PMID: 6482967]
79. Reynolds AJ, Jahoda CA: Cultured dermal papilla cells induce follicle formation and hair growth by transdifferentiation of an adult epidermis. *Development* **115**:587, 1992 [PMID: 1425341]
80. Elliott K, Stephenson TJ, Messenger AG: Differences in hair follicle dermal papilla volume are due to extracellular matrix volume and cell number: Implications for the control of hair follicle size and androgen responses. *J Invest Dermatol* **113**:873, 1999 [PMID: 10594724]

81. Sharov AA et al: BMP signaling controls hair follicle size and modulates the expression of cell cycle-associated genes. *Proc Natl Acad Sci U S A* **103**:18166, 2006 [PMID: 17114283]
82. Danilenko et al: Keratinocyte growth factor is an important endogenous mediator of hair follicle growth, development, and differentiation. Normalization of the nu/nu follicular differentiation defect and amelioration of chemotherapy-induced alopecia. *Am J Pathol* **147**:145, 1995 [PMID: 7604876]
83. Guo L, Degenstein L, Fuchs E: Keratinocyte growth factor is required for hair development but not for wound healing. *Genes Dev* **10**:165, 1996 [PMID: 8566750]
84. Paus R et al: Neural mechanisms of hair growth control. Review. *J Invest Dermatol Symp Proc* **2**:61, 1997 [PMID: 9487018]
85. Halata Z: Sensory innervation of the hairy skin (light- and electronmicroscopic study. *J Invest Dermatol* **101**:75S, 1993
86. Paus R et al: Hair-growth induction by substance P. *Lab Invest* **71**:134, 1994 [PMID: 7518880]
87. Botchkarev VA et al: Hair cycle-dependent changes in adrenergic skin innervation, and hair growth modulation by adrenergic drugs. *J Invest Dermatol* **113**:878, 1999 [PMID: 10594725]
88. Hordinsky M et al: Peribulbar innervation and substance P expression following nonpermanent injury to the human scalp hair follicle. *J Invest Dermatol Symp Proc* **4**:316, 1999 [PMID: 10674389]
89. Hordinsky MK, Ericson ME: Relationship between follicular nerve supply and alopecia. *Dermatol Clin* **14**:651, 1996 [PMID: 9238323]
90. Peters EM et al: Hair-cycle-associated remodeling of the peptidergic innervation of murine skin, and hair growth modulation by neuropeptides. *J Invest Dermatol* **116**:236, 2001 [PMID: 11179999]
91. Botchkarev VA et al: Hair cycle-dependent plasticity of skin and hair follicle innervation in normal murine skin. *J Comp Neurol* **386**:379, 1997 [PMID: 9303424]
92. Narisawa Y et al: A high concentration of Merkel cells in the bulge prior to the attachment of the arrector pili muscle and the formation of the perifollicular nerve plexus in human fetal skin. *Arch Dermatol Res* **285**:261, 1993 [PMID: 8379685]
93. Reynolds AJ et al: Trans-gender induction of hair follicles. *Nature* **402**:33, 1999 [PMID: 10573414]
94. Whiting DA: Chronic telogen effluvium: Increased scalp hair shedding in middle-aged women [see comments]. *J Am Acad Dermatol* **35**:899, 1996 [PMID: 8959948]
95. Cotsarelis G, Sun TT, Lavker RM: Label-retaining cells reside in the bulge area of pilosebaceous unit: Implications for follicular stem cells, hair cycle, and skin carcinogenesis. *Cell* **61**:1329, 1990 [PMID: 2364430]
96. Ito M et al: Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis. *Nat Med* **11**:1351, 2005 [PMID: 16288281]
97. Morris RJ et al: Capturing and profiling adult hair follicle stem cells. *Nat Biotechnol* **22**:411, 2004 [PMID: 15024388]
98. Oshima H et al: Morphogenesis and renewal of hair follicles from adult multipotent stem cells. *Cell* **104**:233, 2001 [PMID: 11207364]
99. Jaks V et al: Lgr5 marks cycling, yet long-lived, hair follicle stem cells. *Nat Genet* **40**:1291. [PMID: 18849992]
100. Snippert HJ et al: Lgr6 marks stem cells in the hair follicle that generate all cell lineages of the skin. *Science*. **327**:1385, 2010 [PMID: 20223988]
101. Jaks V, Kasper M, Toftgård R: The hair follicle—a stem cell zoo. *Exp Cell Res* **316**:1422, 2010. [PMID:20338163]
102. Muller-Rover S et al: A comprehensive guide for the accurate classification of murine hair follicles in distinct hair cycle stages. *J Invest Dermatol* **117**:3, 2001 [PMID: 11442744]
103. Sano S et al: Keratinocyte-specific ablation of Stat3 exhibits impaired skin remodeling, but does not affect skin morphogenesis. *EMBO J* **18**:4657, 1999 [PMID: 10469645]
104. Botchkareva NV et al: SCF/c-kit signaling is required for cyclic regeneration of the hair pigmentation unit. *FASEB J* **15**:645, 2001 [PMID: 11259383]
105. Pierard GE, de la Brassinne M: Modulation of dermal cell activity during hair growth in the rat. *J Cutan Pathol* **2**:35, 1975 [PMID: 1225936]
106. Botchkareva NV, Ahluwalia G, Shander D: Apoptosis in the hair follicle. *J Invest Dermatol* **126**:258, 2006 [PMID: 16418734]
107. Ahmad W et al: Alopecia universalis associated with a mutation in the human hairless gene. *Science* **279**:720, 1998 [PMID: 9445480]
108. Miller J et al: Atrichia caused by mutations in the vitamin D receptor gene is a phenocopy of generalized atrichia caused by mutations in the hairless gene. *J Invest Dermatol* **117**:612, 2001 [PMID: 11564167]

109. Rosenquist TA, Martin GR: Fibroblast growth factor signalling in the hair growth cycle: Expression of the fibroblast growth factor receptor and ligand genes in the murine hair follicle. *Dev Dyn* **205**:379, 1996 [PMID: 8901049]
110. Pena JC et al: Manipulation of outer root sheath cell survival perturbs the hair-growth cycle. *EMBO J* **18**:3596, 1999 [PMID: 10393176]
111. Hollis DE, Chapman RE: Apoptosis in wool follicles during mouse epidermal growth factor (mEGF)-induced catagen regression. *J Invest Dermatol* **88**:455, 1987 [PMID: 3494087]
112. Hansen LA et al: Genetically null mice reveal a central role for epidermal growth factor receptor in the differentiation of the hair follicle and normal hair development. *Am J Pathol* **150**:1959, 1997 [PMID: 9176390]
113. Bol D et al: Severe follicular hyperplasia and spontaneous papilloma formation in transgenic mice expressing the neu oncogene under the control of the bovine keratin 5 promoter. *Mol Carcinog* **21**:2, 1998 [PMID: 9473766]
114. Botchkarev VA et al: Neurotrophin-3 involvement in the regulation of hair follicle morphogenesis. *J Invest Dermatol* **111**:279, 1998 [PMID: 9699730]
115. Botchkarev VA et al: A role for p75 neurotrophin receptor in the control of apoptosis-driven hair follicle regression. *FASEB J* **14**:1931, 2000 [PMID: 11023977]
116. Foitzik K et al: Control of murine hair follicle regression (catagen) by TGF-beta1 in vivo. *FASEB J* **14**:752, 2000 [PMID: 10744631]
117. Philpott MP et al: Human hair growth in vitro: A model for study of hair follicle biology. *J Dermatol Sci* **7**:S55, 1994
118. Blair HJ et al: An integrated genetic and man-mouse comparative map of the DXHXS674-Pdha1 region of the mouse X chromosome. *Genomics* **48**:128, 1998 [PMID: 9503026]
119. Milner Y et al: Exogen, shedding phase of the hair growth cycle: Characterization of a mouse model. *J Invest Dermatol* **119**:639, 2002 [PMID: 12230507]
120. Headington JT: Telogen effluvium. New concepts and review. *Arch Dermatol* **129**:356, 1993 [PMID: 8447677]
121. Guarrera M, Rebora A: Anagen hairs may fail to replace telogen hairs in early androgenic female alopecia. *Dermatology* **192**:28, 1996 [PMID: 8832948]
122. Slominski A et al: Melanin pigmentation in mammalian skin and its hormonal regulation. *Physiol Rev* **84**:1155, 2004 [PMID: 15383650]
123. Magerl M et al: Patterns of proliferation and apoptosis during murine hair follicle morphogenesis. *J Invest Dermatol* **116**:947, 2001 [PMID: 11407986]
124. Tobin D J et al: The fate of hair follicle melanocytes during the hair growth cycle. *J Invest Dermatol* **4**:323, 1999 [PMID: 10674391]
125. Slominski A et al: Hair follicle pigmentation. *J Invest Dermatol* **124**:13, 2005 [PMID: 15654948]
126. Holbrook KA et al: The appearance, density and distribution of melanocytes in human embryonic and fetal skin revealed by the anti-melanoma monoclonal antibody, HMB-45. *Anat Embryol (Berlin)* **80**:443, 1989
127. Jordan S, Beermann F: Nomenclature for identified pigmentation genes in the mouse. *Pigment Cell Res* **13**:70, 2000 [PMID: 10841027]
128. Yoshida H et al: Distinct stages of melanocyte differentiation revealed by analysis of nonuniform pigmentation patterns. *Development* **122**:1207, 1996 [PMID: 8620847]
- 129 **Boissy RE, Nordlund JJ: Molecular basis of congenital hypopigmentary disorders in humans: A review.** *Pigment Cell Res* **10**:12, 1997 [PMID: 9170158]
- 129a. Ernfors P: Cellular origin and developmental mechanisms during the formation of skin melanocytes. *Exp Cell Res* **316**:1397-1407, 2010 [PMID: 20211169]
130. Botchkareva NV, Botchkarev VA, Gilchrist BA: Fate of melanocytes during development of the hair follicle pigmentary unit. *J Invest Dermatol Symp Proc* **8**:76, 2003 [PMID: 12894999]
131. Nishikawa S et al: In utero manipulation of coat color formation by a monoclonal anti-c-kit antibody: Two distinct waves of c-kit-dependency during melanocyte development. *EMBO J* **10**:2111, 1991 [PMID: 1712289]
132. Kunisada T et al: Transgene expression of steel factor in the basal layer of epidermis promotes survival, proliferation, differentiation and migration of melanocyte precursors. *Development* **125**:2915, 1998 [PMID: 9655813]
133. Zsebo KM et al: Stem cell factor is encoded at the Sl locus of the mouse and is the ligand for the c-kit tyrosine kinase receptor. *Cell* **63**:213, 1990 [PMID: 1698556]
134. McGill GG et al: Bcl2 regulation by the melanocyte master regulator Mitf modulates lineage survival and melanoma cell viability. *Cell* **109**:707, 2002 [PMID: 12086670]
135. Mak SS et al: Indispensable role of Bcl2 in the development of the melanocyte stem cell. *Dev Biol* **291**:144, 2006 [PMID: 16427619]

136. Nishimura EK, Granter SR, Fisher DE: Mechanisms of hair graying: Incomplete melanocyte stem cell maintenance in the niche. *Science* **307**:720, 2005 [PMID: 15618488]
137. Nishimura EK, Suzuki M, Igras V et al: Key roles for transforming growth factor beta in melanocyte stem cell maintenance. *Cell Stem Cell* **6**:130-140, 2010 [PMID: 20144786]
138. Moriyama M, Osawa M, Mak SS et al: Notch signaling via Hes1 transcription factor maintains survival of melanoblasts and melanocyte stem cells. *J Cell Biol* **173**:333-339, 2006
139. Veis DJ et al: **Bcl-2-deficient mice demonstrate fulminant lymphoid apoptosis, polycystic kidneys, and hypopigmented hair.** *Cell* **75**:229, 1993 [PMID: 8402909]
140. Yamamura K et al: Accelerated disappearance of melanocytes in bcl-2-deficient mice. *Cancer Res* **56**:3546, 1996 [PMID: 8758925]
141. Commo S, Bernard BA: Melanocyte subpopulation turnover during the human hair cycle: An immunohistochemical study. *Pigment Cell Res* **13**:253, 2000 [PMID: 10952393]
142. Weiner L, Han R, Scicchitano BM, Li J, Hasegawa K, Grossi M, Lee D, Brissette JL: Dedicated epithelial recipient cells determine pigmentation patterns. *Cell* **130**:932, 2007 [PMID:17803914]
143. Sugiyama S et al: **Proliferating activity of the hair follicular melanocytes at the early and anagen III stages in the hair growth cycle: Detection by immunocytochemistry for bromodeoxyuridine combined with DOPA reaction cytochemistry.** *J Dermatol* **22**:396, 1995 [PMID: 7650237]
144. Aubin-Houzelstein G, Djian-Zaouche J, Bernex F, Gadin S, Delmas V, Larue L, Panthier JJ: Melanoblasts' proper location and timed differentiation depend on Notch/RBP-J signaling in postnatal hair follicles. *J Invest Dermatol* **128**:2686, 2008 [PMID: 18463680]
145. Schallreuter KU et al: **Pterins in human hair follicle cells and in the synchronized murine hair cycle.** *J Invest Dermatol* **111**:545, 1998 [PMID: 9764831]
146. Sharov A et al: **Changes in different melanocyte populations during hair follicle involution (catagen).** *J Invest Dermatol* **125**:1259, 2005 [PMID: 16354197]
147. Abdel-Malek ZA et al: The melanocortin-1 receptor and human pigmentation. *Ann N Y Acad Sci* **885**:117, 1999 [PMID: 10816645]
148. Barsh GS: What controls variation in human skin color? *PLoS Biol* **1**:E27, 2003
149. Abdel-Malek ZA: Melanocortin receptors: Their functions and regulation by physiological agonists and antagonists. *Cell Mol Life Sci* **58**:434, 2001 [PMID: 11315190]
150. Ha T et al: Defining the quantitative contribution of the melanocortin 1 receptor (MC1R) to variation in pigimentary phenotype. *Ann N Y Acad Sci* **994**:339, 2003 [PMID: 12851334]
151. Sharov AA et al: Bone morphogenetic protein (BMP) signaling controls hair pigmentation by means of cross-talk with the melanocortin receptor-1 pathway. *Proc Natl Acad Sci U S A* **102**:93, 2005 [PMID: 15618398]
152. Kauser S et al: A fully-functional POMC/MC-1R system regulates the differentiation of human scalp hair follicle melanocytes. *Endocrinology* **146**:532, 2005 [PMID: 15498881]
153. Cable J, Jackson IJ, Steel KP: Light (Blt), a mutation that causes melanocyte death, affects stria vascularis function in the mouse inner ear. *Pigment Cell Res* **6**:215, 1993 [PMID: 8248019]
154. Tobin DJ: Human hair pigmentation—biological aspects. *Int J Cosmet Sci* **30**:233, 2008 [PMID:18713071]
155. Inomata K, Aoto T, Binh NT, et al: Genotoxic stress abrogates renewal of melanocyte stem cells by triggering their differentiation. *Cell* **137**:1088, 2009 [PMID:19524511]
156. Wood JM, Decker H, Hartmann H, et al: Senile hair graying: H<sub>2</sub>O<sub>2</sub>-mediated oxidative stress affects human hair color by blunting methionine sulfoxide repair. *FASEB J* **23**:2065, 2009 [PMID: 19237503]