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ANÁLISIS COMPARATIVO DE LA EXPRESIÓN DE miRNAs EN EL DESARROLLO EMBRIONARIO DEL COLON, EL CÁNCER COLORECTAL Y EL LINFOMA DE HODGKIN

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BIBLIOGRAFÍA

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1. Lee,R.C., Feinbaum,R.L., & Ambros,V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* **75**, 843-854 (1993).

2. Wightman,B., Ha,I., & Ruvkun,G. Posttranscriptional Regulation of the Heterochronic Gene Lin-14 by Lin-4 Mediates Temporal Pattern-Formation in C-Elegans. *Cell* **75**, 855-862 (1993).

3. Lee,R.C. & Ambros,V. An extensive class of small RNAs in Caenorhabditis elegans. *Science* **294**, 862-864 (2001).

4. Lau,N.C., Lim,L.P., Weinstein,E.G., & Bartel,D.P. An abundant class of tiny RNAs with probable regulatory roles in Caenorhabditis elegans. *Science* **294**, 858-862 (2001).

5. Lagos-Quintana,M., Rauhut,R., Lendeckel,W., & Tuschl,T. Identification of novel genes coding for small expressed RNAs. *Science* **294**, 853-858 (2001).

6. Lagos-Quintana,M. *et al.* Identification of tissue-specific microRNAs from mouse. *Current Biology* **12**, 735-739 (2002).

7. Reinhart,B.J. *et al.* The 21-nucleotide let-7 RNA regulates developmental timing in Caenorhabditis elegans. *Nature* **403**, 901-906 (2000).

8. Slack,F.J. *et al.* The lin-41 RBCC gene acts in the C-elegans heterochronic pathway between the let-7 regulatory RNA and the LIN-29 transcription factor. *Molecular Cell* **5**, 659-669 (2000).

9. Pasquinelli,A.E. *et al.* Conservation of the sequence and temporal expression of let-7 heterochronic regulatory RNA. *Nature* **408**, 86-89 (2000).

10. Griffiths-Jones,S. The microRNA Registry. *Nucleic Acids Research* **32**, D109-D111 (2004).

11. Griffiths-Jones,S., Grocock,R.J., van Dongen,S., Bateman,A., & Enright,A.J. miRBase: microRNA sequences, targets and gene nomenclature. *Nucleic Acids Research* **34**, D140-D144 (2006).

12. Rodriguez,A., Griffiths-Jones,S., Ashurst,J.L., & Bradley,A. Identification of mammalian microRNA host genes and transcription units. *Genome Research* **14**, 1902-1910 (2004).

13. Zeng,Y. Principles of micro-RNA production and maturation. *Oncogene* **25**, 6156-6162 (2006).

14. Lin,S.L., Miller,J.D., & Ying,S.Y. IntronicMicroRNA (miRNA). *Journal of Biomedicine and Biotechnology*(2006).

15. Bartel,D.P. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* **116**, 281-297 (2004).

16. Smalheiser,N.R. & Torvik,V.I. Mammalian microRNAs derived from genomic repeats. *Trends in Genetics* **21**, 322-326 (2005).

17. Lee,Y. *et al.* MicroRNA genes are transcribed by RNA polymerase II. *Embo Journal* **23**, 4051-4060 (2004).

18. Cai,X.Z., Hagedorn,C.H., & Cullen,B.R. Human microRNAs are processed from capped, polyadenylated transcripts that can also function as mRNAs. *Rna-A Publication of the Rna Society* **10**, 1957-1966 (2004).

19. Lee,Y. *et al.* The nuclear RNase III Drosha initiates microRNA processing. *Nature* **425**, 415-419 (2003).

20. Denli,A.M., Tops,B.B.J., Plasterk,R.H.A., Ketting,R.F., & Hannon,G.J. Processing of primary microRNAs by the Microprocessor complex. *Nature* **432**, 231-235 (2004).

21. Lund,E., Guttinger,S., Calado,A., Dahlberg,J.E., & Kutay,U. Nuclear export of microRNA precursors. *Science* **303**, 95-98 (2004).

22. Yi,R., Qin,Y., Macara,I.G., & Cullen,B.R. Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs. *Genes & Development* **17**, 3011-3016 (2003).

23. Grishok,A. *et al.* Genes and mechanisms related to RNA interference regulate expression of the small temporal RNAs that control C-elegans developmental timing. *Cell* **106**, 23-34 (2001).

24. Hutvagner,G. *et al.* A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA. *Science* **293**, 834-838 (2001).

25. Khvorova,A., Reynolds,A., & Jayasena,S.D. Functional siRNAs and rniRNAs exhibit strand bias. *Cell* **115**, 209-216 (2003).

26. Schwarz,D.S. *et al.* Asymmetry in the assembly of the RNAi enzyme complex. *Cell* **115**, 199-208 (2003).

27. Bagga,S. *et al.* Regulation by let-7 and lin-4 miRNAs results in target mRNA degradation. *Cell* **122**, 553-563 (2005).

28. Doench,J.G. & Sharp,P.A. Specificity of microRNA target selection in translational repression. *Genes & Development* **18**, 504-511 (2004).

29. Lim,L.P. *et al.* Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. *Nature* **433**, 769-773 (2005).

30. Pillai,R.S. *et al.* Inhibition of translational initiation by Let-7 microRNA in human cells. *Science* **309**, 1573-1576 (2005).

31. Hutvagner,G. & Zamore,P.D. A microRNA in a multiple-turnover RNAi enzyme complex. *Science* **297**, 2056-2060 (2002).

32. Jopling,C.L., Yi,M.K., Lancaster,A.M., Lemon,S.M., & Sarnow,P. Modulation of hepatitis C virus RNA abundance by a liver-specific microRNA. *Science* **309**, 1577-1581 (2005).

33. Chu,C.Y. & Rana,T.M. Translation repression in human cells by microRNA-induced gene silencing requires RCK/p54. *Plos Biology* **4**, 1122-1136 (2006).

34. Sen,G.L. & Blau,H.M. Argonaute 2/RISC resides in sites of mammalian mRNA decay known as cytoplasmic bodies. *Nature Cell Biology* **7**, 633-U28 (2005).

35. Liu,J.D., Valencia-Sanchez,M.A., Hannon,G.J., & Parker,R. MicroRNA-dependent localization of targeted mRNAs to mammalian P-bodies. *Nature Cell Biology* **7**, 719-U118 (2005).

36. Valencia-Sanchez,M.A., Liu,J.D., Hannon,G.J., & Parker,R. Control of translation and mRNA degradation by miRNAs and siRNAs. *Genes & Development* **20**, 515-524 (2006).

37. Lewis,B.P., Burge,C.B., & Bartel,D.P. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell* **120**, 15-20 (2005).

38. Fire,A. *et al.* Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. *Nature* **391**, 806-811 (1998).

39. Williams,B.R.G. Role of the double-stranded RNA-activated protein kinase (PKR) in cell regulation. *Biochemical Society Transactions* **25**, 509-513 (1997).

40. Caplen,N.J., Parrish,S., Imani,F., Fire,A., & Morgan,R.A. Specific inhibition of gene expression by small double-stranded RNAs in invertebrate and vertebrate systems. *Proceedings of the National Academy of Sciences of the United States of America* **98**, 9742-9747 (2001).

41. Elbashir,S.M. *et al.* Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells. *Nature* **411**, 494-498 (2001).

42. Tolia,N.H. & Joshua-Tor,L. Slicer and the Argonautes. *Nature Chemical Biology* **3**, 36-43 (2007).

43. Rana,T.M. Illuminating the silence: understanding the structure and function of small RNAs. *Nature Reviews Molecular Cell Biology* **8**, 23-36 (2007).

44. Brennecke,J., Hipfner,D.R., Stark,A., Russell,R.B., & Cohen,S.M. bantam encodes a developmentally regulated microRNA that controls cell proliferation and regulates the proapoptotic gene hid in Drosophila. *Cell* **113**, 25-36 (2003).

45. Rajewsky,N. & Socci,N.D. Computational identification of microRNA targets. *Developmental Biology* **267**, 529-535 (2004).

46. Lewis,B.P., Shih,I.H., Jones-Rhoades,M.W., Bartel,D.P., & Burge,C.B. Prediction of mammalian microRNA targets. *Cell* **115**, 787-798 (2003).

47. Krek,A. *et al.* Combinatorial microRNA target predictions. *Nature Genetics* **37**, 495-500 (2005).

48. Brennecke,J., Stark,A., Russell,R.B., & Cohen,S.M. Principles of MicroRNA-target recognition. *Plos Biology* **3**, 404-418 (2005).

49. Xie,X.H. *et al.* Systematic discovery of regulatory motifs in human promoters and 3 ' UTRs by comparison of several mammals. *Nature* **434**, 338-345 (2005).

50. Robins,H., Li,Y., & Padgett,R.W. Incorporating structure to predict microRNA targets. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 4006-4009 (2005).

51. Doench,J.G. & Sharp,P.A. Specificity of microRNA target selection in translational repression. *Genes & Development* **18**, 504-511 (2004).

52. Krek,A. *et al.* Combinatorial microRNA target predictions. *Nature Genetics* **37**, 495-500 (2005).

53. Stark,A., Brennecke,J., Bushati,N., Russell,R.B., & Cohen,S.M. Animal microRNAs confer robustness to gene expression and have a significant impact on 3 ' UTR evolution. *Cell* **123**, 1133-1146 (2005).

54. Krutzfeldt,J. *et al.* Silencing of microRNAs in vivo with 'antagomirs'. *Nature* **438**, 685-689 (2005).

55. Bartel,D.P. & Chen,C.Z. Micromanagers of gene expression: the potentially widespread influence of metazoan microRNAs. *Nature Reviews Genetics* **5**, 396-400 (2004).

56. Lall,S. *et al.* A genome-wide map of conserved microRNA targets in C. elegans. *Current Biology* **16**, 460-471 (2006).

57. Berezikov,E. *et al.* Phylogenetic shadowing and computational identification of human microRNA genes. *Cell* **120**, 21-24 (2005).

58. Calin,G.A. *et al.* A MicroRNA signature associated with prognosis and progression in chronic lymphocytic leukemia. *N. Engl. J. Med.* **353**, 1793-1801 (2005).

59. Yoo,A.S. & Greenwald,I. LIN-12/Notch activation leads to microRNA-mediated down-regulation of Vav in C. elegans. *Science* **310**, 1330-1333 (2005).

60. Saito,Y. *et al.* Specific activation of microRNA-127 with downregulation of the proto-oncogene BCL6 by chromatin-modifying drugs in human cancer cells. *Cancer Cell* **9**, 435-443 (2006).

61. Scott,G.K., Mattie,N.D., Berger,C.E., Benz,S.C., & Benz,C.C. Rapid alteration of microRNA levels by histone deacetylase inhibition. *Cancer Research* **66**, 1277-1281 (2006).

62. Kim,V.N. & Nam,J.W. Genomics of microRNA. *Trends in Genetics* **22**, 165-173 (2006).

63. Ying,S.Y. & Lin,S.L. Intronic microRNAs. *Biochemical and Biophysical Research Communications* **326**, 515-520 (2005).

64. Hatfield,S.D. *et al.* Stem cell division is regulated by the microRNA pathway. *Nature* **435**, 974-978 (2005).

65. Knight,S.W. & Bass,B.L. A role for the RNase III enzyme DCR-1 in RNA interference and germ line development in Caenorhabditis elegans. *Science* **293**, 2269-2271 (2001).

66. Lee,Y.S. *et al.* Distinct roles for Drosophila Dicer-1 and Dicer-2 in the siRNA/miRNA silencing pathways. *Cell* **117**, 69-81 (2004).

67. Wienholds,E., Koudijs,M.J., van Eeden,F.J.M., Cuppen,E., & Plasterk,R.H.A. The microRNA-producing enzyme Dicer1 is essential for zebrafish development. *Nature Genetics* **35**, 217-218 (2003).

68. Bernstein,E. *et al.* Dicer is essential for mouse development. *Nature Genetics* **35**, 215-217 (2003).

69. Liu,J.D. *et al.* Argonaute2 is the catalytic engine of mammalian RNAi. *Science* **305**, 1437-1441 (2004).

70. Lu,J.I. *et al.* Differential expression of components of the microRNA machinery during mouse organogenesis. *Biochemical and Biophysical Research Communications* **334**, 319-323 (2005).

71. Harfe,B.D., McManus,M.T., Mansfield,J.H., Hornstein,E., & Tabin,C.J. The RNaseIII enzyme Dicer is required for morphogenesis but not patterning of the vertebrate limb. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 10898-10903 (2005).

72. Yekta,S., Shih,I.H., & Bartel,D.P. MicroRNA-directed cleavage of HOXB8 mRNA. *Science* **304**, 594-596 (2004).

73. Hornstein,E. *et al.* The microRNA miR-196 acts upstream of Hoxb8 and Shh in limb development. *Nature* **438**, 671-674 (2005).

74. Mineno,J. *et al.* The expression profile of microRNAs in mouse embryos. *Nucleic Acids Research* **34**, 1765-1771 (2006).

75. Houbaviy,H.B., Murray,M.F., & Sharp,P.A. Embryonic stem cell-specific MicroRNAs. *Developmental Cell* **5**, 351-358 (2003).

76. Suh,M.R. *et al.* Human embryonic stem cells express a unique set of microRNAs. *Developmental Biology* **270**, 488-498 (2004).

77. Tang,F.C., Hajkova,P., Barton,S.C., Lao,K.Q., & Surani,M.A. MicroRNA expression profiling of single whole embryonic stem cells. *Nucleic Acids Research* **34**, (2006).

78. Hallam,S.J. & Jin,Y. lin-14 regulates the timing of synaptic remodelling in Caenorhabditis elegans. *Nature* **395**, 78-82 (1998).

79. Johnston,R.J. & Hobert,O. A microRNA controlling left/right neuronal asymmetry in Caenorhabditis elegans. *Nature* **426**, 845-849 (2003).

80. Schratt,G.M. *et al.* A brain-specific microRNA regulates dendritic spine development. *Nature* **439**, 283-289 (2006).

81. Sokol,N.S. & Ambros,V. Mesodermally expressed Drosophila microRNA-1 is regulated by Twist and is required in muscles during larval growth. *Genes & Development* **19**, 2343-2354 (2005).

82. Zhao,Y., Samal,E., & Srivastava,D. Serum response factor regulates a muscle-specific microRNA that targets Hand2 during cardiogenesis. *Nature* **436**, 214-220 (2005).

83. Chen,J.F. *et al.* The role of microRNA-1 and microRNA-133 in skeletal muscle proliferation and differentiation. *Nature Genetics* **38**, 228-233 (2006).

84. Chen,C.Z. & Lodish,H.F. MicroRNAs as regulators of mammalian hematopoiesis. *Seminars in Immunology* **17**, 155-165 (2005).

85. Ambros,V. MicroRNA pathways in flies and worms: Growth, death, fat, stress, and timing. *Cell* **113**, 673-676 (2003).

86. Harris,K.S., Zhang,Z., McManus,M.T., Harfe,B.D., & Sun,X. Dicer function is essential for lung epithelium morphogenesis. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 2208-2213 (2006).

87. Calin,G.A. *et al.* Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proc. Natl. Acad. Sci. U. S. A* **101**, 2999-3004 (2004).

88. Calin,G.A. & Croce,C.M. MicroRNA signatures in human cancers. *Nat. Rev. Cancer* **6**, 857-866 (2006).

89. Lu,J. *et al.* MicroRNA expression profiles classify human cancers. *Nature* **435**, 834-838 (2005).

90. Takamizawa,J. *et al.* Reduced expression of the let-7 microRNAs in human lung cancers in association with shortened postoperative survival. *Cancer Research* **64**, 3753-3756 (2004).

91. Johnson,S.M. *et al.* RAS is regulated by the let-7 MicroRNA family. *Cell* **120**, 635-647 (2005).

92. Voorhoeve,P.M. *et al.* A genetic screen implicates miRNA-372 and miRNA-373 as oncogenes in testicular germ cell tumors. *Cell* **124**, 1169-1181 (2006).

93. Ota,A. *et al.* Identification and characterization of a novel gene, C13orf25, as a target for 13q31-q32 amplification in malignant lymphoma. *Cancer Research* **64**, 3087-3095 (2004).

94. O'Donnell,K.A., Wentzel,E.A., Zeller,K.I., Dang,C.V., & Mendell,J.T. c-Myc-regulated microRNAs modulate E2F1 expression. *Nature* **435**, 839-843 (2005).

95. Sylvestre,Y. *et al.* An E2F/miR-20a autoregulatory feedback loop. *Journal of Biological Chemistry* **282**, 2135-2143 (2007).

96. Woods,K., Thomson,J.M., & Hammond,S.M. Direct regulation of an oncogenic micro-RNA cluster by E2F transcription factors. *Journal of Biological Chemistry* **282**, 2130-2134 (2007).

97. Iorio,M.V. *et al.* MicroRNA gene expression deregulation in human breast cancer. *Cancer Research* **65**, 7065-7070 (2005).

98. Chan,J.A., Krichevsky,A.M., & Kosik,K.S. MicroRNA-21 is an antiapoptotic factor in human glioblastoma cells. *Cancer Research* **65**, 6029-6033 (2005).

99. Lee,E.J. *et al.* Expression profiling identifies microRNA signature in pancreatic cancer. *International Journal of Cancer* **120**, 1046-1054 (2007).

100. Roldo,C. *et al.* MicroRNA expression abnormalities in pancreatic endocrine and acinar tumors are associated with distinctive pathologic features and clinical behavior. *Journal of Clinical Oncology* **24**, 4677-4684 (2006).

101. Si,M.L. *et al.* miR-21-mediated tumor growth. *Oncogene* **26**, 2799-2803 (2007).

102. Meng,F. *et al.* MicroRNA-21 regulation of survival signaling: A novel mechanism of chemoresistance in cholangiocarcincoma. *Gastroenterology* **130**, A429 (2006).

103. Yonaihara,N. *et al.* Unique microRNA molecular profiles in lung cancer diagnosis and prognosis. *Cancer Cell* **9**, 189-198 (2006).

104. Volinia,S. *et al.* A microRNA expression signature of human solid tumors defines cancer gene targets. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 2257-2261 (2006).

105. Ramkissoon,S.H. *et al.* Hematopoietic-specific microRNA expression in human cells. *Leuk. Res.* **30**, 643-647 (2006).

106. Monticelli,S. *et al.* MicroRNA profiling of the murine hematopoietic system. *Genome Biol.* **6**, R71 (2005).

107. Felli,N. *et al.* MicroRNAs 221 and 222 inhibit normal erythropoiesis and erythroleukemic cell growth via kit receptor down-modulation. *Proc. Natl. Acad. Sci. U. S. A* **102**, 18081-18086 (2005).

108. Fazi,F. *et al.* A minicircuitry comprised of microRNA-223 and transcription factors NFI-A and C/EBPalpha regulates human granulopoiesis. *Cell* **123**, 819-831 (2005).

109. Garzon,R. *et al.* MicroRNA fingerprints during human megakaryocytopoiesis. *Proc. Natl. Acad. Sci. U. S. A* **103**, 5078-5083 (2006).

110. Georgantas,R.W., III *et al.* CD34+ hematopoietic stem-progenitor cell microRNA expression and function: a circuit diagram of differentiation control. *Proc. Natl. Acad. Sci. U. S. A* **104**, 2750-2755 (2007).

111. Cobb,B.S. *et al.* T cell lineage choice and differentiation in the absence of the RNase III enzyme Dicer. *J. Exp. Med.* **201**, 1367-1373 (2005).

112. Muljo,S.A. *et al.* Aberrant T cell differentiation in the absence of Dicer. *J. Exp. Med.* **202**, 261-269 (2005).

113. Kanellopoulou,C. *et al.* Dicer-deficient mouse embryonic stem cells are defective in differentiation and centromeric silencing. *Genes Dev.* **19**, 489-501 (2005).

114. Calin,G.A. *et al.* MicroRNA profiling reveals distinct signatures in B cell chronic lymphocytic leukemias. *Proc. Natl. Acad. Sci. U. S. A* **101**, 11755-11760 (2004).

115. Cimmino,A. *et al.* miR-15 and miR-16 induce apoptosis by targeting BCL2. *Proc. Natl. Acad. Sci. U. S. A* **102**, 13944-13949 (2005).

116. Pekarsky,Y. *et al.* Tcl1 expression in chronic lymphocytic leukemia is regulated by miR-29 and miR-181. *Cancer Res.* **66**, 11590-11593 (2006).

117. Garzon,R. *et al.* MicroRNA gene expression during retinoic acid-induced differentiation of human acute promyelocytic leukemia. *Oncogene* **26**, 4148-4157 (2007).

118. Gauwerky,C.E., Huebner,K., Isobe,M., Nowell,P.C., & Croce,C.M. Activation of MYC in a masked t(8;17) translocation results in an aggressive B-cell leukemia. *Proc. Natl. Acad. Sci. U. S. A* **86**, 8867-8871 (1989).

119. Sonoki,T., Iwanaga,E., Mitsuya,H., & Asou,N. Insertion of microRNA-125b-1, a human homologue of lin-4, into a rearranged immunoglobulin heavy chain gene locus in a patient with precursor B-cell acute lymphoblastic leukemia. *Leukemia* **19**, 2009-2010 (2005).

120. Venturini,L. *et al.* Expression of the miR-17-92 polycistron in chronic myeloid leukemia (CML) CD34+ cells. *Blood* **109**, 4399-4405 (2007).

121. van den,B.A. *et al.* High expression of B-cell receptor inducible gene BIC in all subtypes of Hodgkin lymphoma. *Genes Chromosomes. Cancer* **37**, 20-28 (2003).

122. Metzler,M., Wilda,M., Busch,K., Viehmann,S., & Borkhardt,A. High expression of precursor microRNA-155/BIC RNA in children with Burkitt lymphoma. *Genes Chromosomes. Cancer* **39**, 167-169 (2004).

123. Eis,P.S. *et al.* Accumulation of miR-155 and BIC RNA in human B cell lymphomas. *Proc. Natl. Acad. Sci. U. S. A* **102**, 3627-3632 (2005).

124. Kluiver,J. *et al.* Lack of BIC and microRNA miR-155 expression in primary cases of Burkitt lymphoma. *Genes Chromosomes. Cancer* **45**, 147-153 (2006).

125. Kluiver,J. *et al.* BIC and miR-155 are highly expressed in Hodgkin, primary mediastinal and diffuse large B cell lymphomas. *J. Pathol.* **207**, 243-249 (2005).

126. O'Connell,R.M., Taganov,K.D., Boldin,M.P., Cheng,G., & Baltimore,D. MicroRNA-155 is induced during the macrophage inflammatory response. *Proc. Natl. Acad. Sci. U. S. A* **104**, 1604-1609 (2007).

127. He,L. *et al.* A microRNA polycistron as a potential human oncogene. *Nature* **435**, 828-833 (2005).

128. Lawrie,C.H. *et al.* Microrna expression distinguishes between germinal center B cell-like and activated B cell-like subtypes of diffuse large B cell lymphoma. *Int. J. Cancer*(2007).

129. Lim,L.P. *et al.* Microarray analysis shows that some microRNAs downregulate large numbers of target mRNAs. *Nature* **433**, 769-773 (2005).

130. Pfeffer,S. *et al.* Identification of virus-encoded microRNAs. *Science* **304**, 734-736 (2004).

131. Cai,X. *et al.* Epstein-Barr virus microRNAs are evolutionarily conserved and differentially expressed. *PLoS. Pathog.* **2**, e23 (2006).

132. Pfeffer,S. *et al.* Identification of microRNAs of the herpesvirus family. *Nat. Methods* **2**, 269-276 (2005).

133. Cai,X. *et al.* Kaposi's sarcoma-associated herpesvirus expresses an array of viral microRNAs in latently infected cells. *Proc. Natl. Acad. Sci. U. S. A* **102**, 5570-5575 (2005).

134. Grey,F. *et al.* Identification and characterization of human cytomegalovirus-encoded microRNAs. *J. Virol.* **79**, 12095-12099 (2005).

135. Samols,M.A., Hu,J., Skalsky,R.L., & Renne,R. Cloning and identification of a microRNA cluster within the latency-associated region of Kaposi's sarcoma-associated herpesvirus. *J. Virol.* **79**, 9301-9305 (2005).

136. Cai,X., Li,G., Laimins,L.A., & Cullen,B.R. Human papillomavirus genotype 31 does not express detectable microRNA levels during latent or productive virus replication. *J. Virol.* **80**, 10890-10893 (2006).

137. Cai,X. & Cullen,B.R. Transcriptional origin of Kaposi's sarcoma-associated herpesvirus microRNAs. *J. Virol.* **80**, 2234-2242 (2006).

138. Gupta,A., Gartner,J.J., Sethupathy,P., Hatzigeorgiou,A.G., & Fraser,N.W. Anti-apoptotic function of a microRNA encoded by the HSV-1 latency-associated transcript. *Nature* **442**, 82-85 (2006).

139. Sullivan,C.S., Grundhoff,A.T., Tevethia,S., Pipas,J.M., & Ganem,D. SV40-encoded microRNAs regulate viral gene expression and reduce susceptibility to cytotoxic T cells. *Nature* **435**, 682-686 (2005).

140. Furnari,F.B., Adams,M.D., & Pagano,J.S. Unconventional processing of the 3' termini of the Epstein-Barr virus DNA polymerase mRNA. *Proc. Natl. Acad. Sci. U. S. A* **90**, 378-382 (1993).

141. Lecellier,C.H. *et al.* A cellular microRNA mediates antiviral defense in human cells. *Science* **308**, 557-560 (2005).

142. Jopling,C.L., Yi,M., Lancaster,A.M., Lemon,S.M., & Sarnow,P. Modulation of hepatitis C virus RNA abundance by a liver-specific MicroRNA. *Science* **309**, 1577-1581 (2005).

143. Wurdinger,T. & Costa,F.F. Molecular therapy in the microRNA era. *Pharmacogenomics J*(2006).

144. Boyle,P. & Ferlay,J. Cancer incidence and mortality in Europe, 2004. *Annals of Oncology* **16**, 481-488 (2005).

145. O'Connell,J.B., Maggard,M.A., & Ko,C.Y. The new AJCC 6 staging system for colon cancer - Does it prognosticate correctly. *Annals of Surgical Oncology* **11**, S68 (2004).

146. Jemal,A. *et al.* Cancer statistics, 2005. *Ca-A Cancer Journal for Clinicians* **55**, 10-30 (2005).

147. Hermanek,P. Evaluation of New Prognostic Factors in Oncology. *Virchows Archiv-An International Journal of Pathology* **427**, 335-336 (1995).

148. Hermanek,P., Wiebelt,H., Staimmer,D., & Riedl,S. Prognostic Factors of Rectum Carcinoma - Experience of the German Multicenter Study Sgcrc. *Tumori* **81**, 60-64 (1995).

149. Midgley,R. & Kerr,D. Adjuvant chemotherapy for stage II colorectal cancer: who should receive therapy and with what? *Ejc Supplements* **3**, 283-289 (2005).

150. Midgley,R. & Kerr,D.J. Adjuvant chemotherapy for stage II colorectal cancer: the time is right! *Nature Clinical Practice Oncology* **2**, 364-369 (2005).

151. Johnston,P.G. Stage II colorectal cancer: To treat or not to treat. *Oncologist* **10**, 332-334 (2005).

152. Calaluce,R., Miedema,B.W., & Yesus,Y.W. Micrometastasis in colorectal carcinoma: A review. *Journal of Surgical Oncology* **67**, 194-202 (1998).

153. Lynch,H.T. & de la Chapelle,A. Genomic medicine - Hereditary colorectal cancer. *New England Journal of Medicine* **348**, 919-932 (2003).

154. Alexander,J. *et al.* Histopathological identification of colon cancer with microsatellite instability. *American Journal of Pathology* **158**, 527-535 (2001).

155. Thibodeau,S.N., Bren,G., & Schaid,D. Microsatellite Instability in Cancer of the Proximal Colon. *Science* **260**, 816-819 (1993).

156. Bronner,C.E. *et al.* Mutation in the Dna Mismatch Repair Gene Homolog Hmlh1 Is Associated with Hereditary Nonpolyposis Colon-Cancer. *Nature* **368**, 258-261 (1994).

157. Leach,F.S. *et al.* Mutations of A Muts Homolog in Hereditary Nonpolyposis Colorectal-Cancer. *Cell* **75**, 1215-1225 (1993).

158. Miyaki,M. *et al.* Germline mutation of MSH6 as the cause of hereditary nonpolyposis colorectal cancer. *Nature Genetics* **17**, 271-272 (1997).

159. Nicolaides,N.C. *et al.* Mutations of 2 Pms Homologs in Hereditary Nonpolyposis Colon-Cancer. *Nature* **371**, 75-80 (1994).

160. Papadopoulos,N. *et al.* Mutation of A Mutl Homolog in Hereditary Colon-Cancer. *Science* **263**, 1625-1629 (1994).

161. Rampino,N. *et al.* Somatic frameshift mutations in the BAX gene in colon cancers of the microsatellite mutator phenotype. *Science* **275**, 967-969 (1997).

162. Huang,J. *et al.* APC mutations in colorectal tumors with mismatch repair deficiency. *Proceedings of the National Academy of Sciences of the United States of America* **93**, 9049-9054 (1996).

163. Haggitt,R.C. & Reid,B.J. Hereditary gastrointestinal polyposis syndromes. *Am. J. Surg. Pathol.* **10**, 871-887 (1986).

164. Howe,J.R., Mitros,F.A., & Summers,R.W. The risk of gastrointestinal carcinoma in familial juvenile polyposis. *Ann. Surg. Oncol.* **5**, 751-756 (1998).

165. Howe,J.R. *et al.* Germline mutations of the gene encoding bone morphogenetic protein receptor 1A in juvenile polyposis. *Nat. Genet.* **28**, 184-187 (2001).

166. Hemminki,A. *et al.* Localization of a susceptibility locus for Peutz-Jeghers syndrome to 19p using comparative genomic hybridization and targeted linkage analysis. *Nat. Genet.* **15**, 87-90 (1997).

167. Jemal,A., Thomas,A., Murray,T., & Thun,M. Cancer statistics, 2002. *CA Cancer J. Clin.* **52**, 23-47 (2002).

168. Fearon,E.R. & Vogelstein,B. A genetic model for colorectal tumorigenesis. *Cell* **61**, 759-767 (1990).

169. Cheng,L. & Lai,M.D. Aberrant crypt foci as microscopic precursors of colorectal cancer. *World J. Gastroenterol.* **9**, 2642-2649 (2003).

170. Nucci,M.R., Robinson,C.R., Longo,P., Campbell,P., & Hamilton,S.R. Phenotypic and genotypic characteristics of aberrant crypt foci in human colorectal mucosa. *Human Pathology* **28**, 1396-1407 (1997).

171. Shih,L.M. *et al.* Top-down morphogenesis of colorectal tumors. *Proceedings of the National Academy of Sciences of the United States of America* **98**, 2640-2645 (2001).

172. Preston,S.L. *et al.* Bottom-up histogenesis of colorectal adenomas: Origin in the monocryptal adenoma and initial expansion by crypt fission. *Cancer Research* **63**, 3819-3825 (2003).

173. Iacopetta,B. TP53 mutation in colorectal cancer. *Human Mutation* **21**, 271-276 (2003).

174. Cahill,D.P., Kinzler,K.W., Vogelstein,B., & Lengauer,C. Genetic instability and darwinian selection in tumours. *Trends in Biochemical Sciences* **24**, M57-M60 (1999).

175. Reya,T. & Clevers,H. Wnt signalling in stem cells and cancer. *Nature* **434**, 843-850 (2005).

176. Bienz,M. & Clevers,H. Linking colorectal cancer to Wnt signaling. *Cell* **103**, 311-320 (2000).

177. Kinzler,K.W. & Vogelstein,B. Lessons from hereditary colorectal cancer. *Cell* **87**, 159-170 (1996).

178. Booth,C., Brady,G., & Potten,C.S. Crowd control in the crypt. *Nature Medicine* **8**, 1360-1361 (2002).

179. Korinek,V. *et al.* Depletion of epithelial stem-cell compartments in the small intestine of mice lacking Tcf-4. *Nature Genetics* **19**, 379-383 (1998).

180. Batlle,E. *et al.* beta-catenin and TCF mediate cell positioning in the intestinal epithelium by controlling the expression of EphB/EphrinB. *Cell* **111**, 251-263 (2002).

181. van de Wetering,M. *et al.* The beta-catenin/TCF-4 complex imposes a crypt progenitor phenotype on colorectal cancer cells. *Cell* **111**, 241-250 (2002).

182. Munemitsu,S., Albert,I., Souza,B., Rubinfeld,B., & Polakis,P. Regulation of Intracellular Beta-Catenin Levels by the Adenomatous Polyposis-Coli (Apc) Tumor-Suppressor Protein. *Proceedings of the National Academy of Sciences of the United States of America* **92**, 3046-3050 (1995).

183. Rubinfeld,B. *et al.* Binding of GSK3 beta to the APC-beta-catenin complex and regulation of complex assembly. *Science* **272**, 1023-1026 (1996).

184. Korinek,V. *et al.* Constitutive transcriptional activation by a beta-catenin-Tcf complex in APC(-/-) colon carcinoma. *Science* **275**, 1784-1787 (1997).

185. Morin,P.J. *et al.* Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC. *Science* **275**, 1787-1790 (1997).

186. Shi,Y.G. & Massague,J. Mechanisms of TGF-beta signaling from cell membrane to the nucleus. *Cell* **113**, 685-700 (2003).

187. Eppert,K. *et al.* MADR2 maps to 18q21 and encodes a TGF beta-regulated MAD-related protein that is functionally mutated in colorectal carcinoma. *Cell* **86**, 543-552 (1996).

188. Takagi,Y. *et al.* Somatic alterations of the DPC4 gene in human colorectal cancers in vivo. *Gastroenterology* **111**, 1369-1372 (1996).

189. Hancock,J.F. Ras proteins: Different signals from different locations. *Nature Reviews Molecular Cell Biology* **4**, 373-384 (2003).

190. Malumbres,M. & Barbacid,M. RAS oncogenes: The first 30 years (vol 3, pg 459, 2003). *Nature Reviews Cancer* **3**, 708 (2003).

191. Andreyev,H.J.N. *et al.* Kirsten ras mutations in patients with colorectal cancer: the 'RASCAL II' study. *British Journal of Cancer* **85**, 692-696 (2001).

192. Rajagopalan,H. *et al.* Tumorigenesis - RAF/RAS oncogenes and mismatch-repair status. *Nature* **418**, 934 (2002).

193. Vogelstein,B. *et al.* Genetic Alterations During Colorectal-Tumor Development. *New England Journal of Medicine* **319**, 525-532 (1988).

194. Baas,A.F. *et al.* Complete polarization of single intestinal epithelial cells upon activation of LKB1 by STRAD. *Cell* **116**, 457-466 (2004).

195. Baas,A.F. *et al.* Activation of the tumour suppressor kinase LKB1 by the STE20-like pseudokinase STRAD. *Embo Journal* **22**, 3062-3072 (2003).

196. Baas,A.F. *et al.* Complete polarization of single intestinal epithelial cells upon activation of LKB1 by STRAD. *Cell* **116**, 457-466 (2004).

197. Baron,M. An overview of the Notch signalling pathway. *Seminars in Cell & Developmental Biology* **14**, 113-119 (2003).

198. Sancho,E., Batlle,E., & Clevers,H. Live and let die in the intestinal epithelium. *Current Opinion in Cell Biology* **15**, 763-770 (2003).

199. Schroder,N. & Gossler,A. Expression of Notch pathway components in fetal and adult mouse small intestine. *Gene Expr. Patterns.* **2**, 247-250 (2002).

200. Ingham,P.W. & McMahon,A.P. Hedgehog signaling in animal development: paradigms and principles. *Genes Dev.* **15**, 3059-3087 (2001).

201. Monzo,M. *et al.* Sonic hedgehog mRNA expression by real-time quantitative PCR in normal and tumor tissues from colorectal cancer patients. *Cancer Letters* **233**, 117-123 (2006).

202. Jaffe,E.S. World Health Organization Classification of Tumours. Pathology and genetics of tumours of hematopoietic and lymphoid tissues.IARC Press:Lyon 2001. 2001.
Ref Type: Generic

203. Maclennan,K.A. *et al.* Relationship of Histopathologic Features to Survival and Relapse in Nodular Sclerosing Hodgkins-Disease - A Study of 1659 Patients. *Cancer* **64**, 1686-1693 (1989).

204. Hess,J.L., Bodis,S., Pinkus,G., Silver,B., & Mauch,P. Histopathologic Grading of Nodular Sclerosis Hodgkins-Disease - Lack of Prognostic-Significance in 254 Surgically Staged Patients. *Cancer* **74**, 708-714 (1994).

205. vanSpronsen,D.J. *et al.* Disappearance of prognostic significance of histopathological grading of nodular sclerosing Hodgkin's disease for unselected patients, 1972-92. *British Journal of Haematology* **96**, 322-327 (1997).

206. Gulley,M.L. *et al.* Epstein-Barr-Virus Dna Is Abundant and Monoclonal in the Reed-Sternberg Cells of Hodgkins-Disease - Association with Mixed

Cellularity Subtype and Hispanic American Ethnicity. *Blood* **83**, 1595-1602 (1994).

207. Braeuninger,A. *et al.* Hodgkin and Reed-Sternberg cells in lymphocyte predominant Hodgkin disease represent clonal populations of germinal center-derived tumor B cells. *Proc. Natl. Acad. Sci. U. S. A* **94**, 9337-9342 (1997).

208. Kanzler,H., Kuppers,R., Hansmann,M.L., & Rajewsky,K. Hodgkin and Reed-Sternberg cells in Hodgkin's disease represent the outgrowth of a dominant tumor clone derived from (crippled) germinal center B cells. *J. Exp. Med.* **184**, 1495-1505 (1996).

209. Kuppers,R. *et al.* Hodgkin disease: Hodgkin and Reed-Sternberg cells picked from histological sections show clonal immunoglobulin gene rearrangements and appear to be derived from B cells at various stages of development. *Proc. Natl. Acad. Sci. U. S. A* **91**, 10962-10966 (1994).

210. Marafioti,T. *et al.* Origin of nodular lymphocyte-predominant Hodgkin's disease from a clonal expansion of highly mutated germinal-center B cells. *N. Engl. J. Med.* **337**, 453-458 (1997).

211. Marafioti,T. *et al.* Hodgkin and reed-sternberg cells represent an expansion of a single clone originating from a germinal center B-cell with functional immunoglobulin gene rearrangements but defective immunoglobulin transcription. *Blood* **95**, 1443-1450 (2000).

212. Jox,A. *et al.* Somatic mutations within the untranslated regions of rearranged Ig genes in a case of classical Hodgkin's disease as a potential cause for the absence of Ig in the lymphoma cells. *Blood* **93**, 3964-3972 (1999).

213. Kuppers,R. Molecular biology of Hodgkin's lymphoma. *Adv. Cancer Res.* **84**, 277-312 (2002).

214. Kuppers,R., Schwering,I., Brauninger,A., Rajewsky,K., & Hansmann,M.L. Biology of Hodgkin's lymphoma. *Ann. Oncol.* **13 Suppl 1**, 11-18 (2002).

215. Re,D. *et al.* Oct-2 and Bob-1 deficiency in Hodgkin and Reed Sternberg cells. *Cancer Res.* **61**, 2080-2084 (2001).

216. Stein,H. *et al.* Down-regulation of BOB.1/OBF.1 and Oct2 in classical Hodgkin disease but not in lymphocyte predominant Hodgkin disease correlates with immunoglobulin transcription. *Blood* **97**, 496-501 (2001).

217. Theil,J. *et al.* Defective octamer-dependent transcription is responsible for silenced immunoglobulin transcription in Reed-Sternberg cells. *Blood* **97**, 3191-3196 (2001).

218. Torlakovic,E., Tierens,A., Dang,H.D., & Delabie,J. The transcription factor PU.1, necessary for B-cell development is expressed in lymphocyte

predominance, but not classical Hodgkin's disease. *Am. J. Pathol.* **159**, 1807-1814 (2001).

219. Jundt,F. *et al.* Loss of PU.1 expression is associated with defective immunoglobulin transcription in Hodgkin and Reed-Sternberg cells of classical Hodgkin disease. *Blood* **99**, 3060-3062 (2002).

220. Ushmorov,A. *et al.* Epigenetic silencing of the immunoglobulin heavy-chain gene in classical Hodgkin lymphoma-derived cell lines contributes to the loss of immunoglobulin expression. *Blood* **104**, 3326-3334 (2004).

221. Lam,K.P., Kuhn,R., & Rajewsky,K. In vivo ablation of surface immunoglobulin on mature B cells by inducible gene targeting results in rapid cell death. *Cell* **90**, 1073-1083 (1997).

222. Liu,Y.J. *et al.* Germinal center cells express bcl-2 protein after activation by signals which prevent their entry into apoptosis. *Eur. J. Immunol.* **21**, 1905-1910 (1991).

223. Wang,J. & Taylor,C.R. Apoptosis and cell cycle-related genes and proteins in classical Hodgkin lymphoma: application of tissue microarray technique. *Appl. Immunohistochem. Mol. Morphol.* **11**, 206-213 (2003).

224. Flavell,K.J. & Murray,P.G. Hodgkin's disease and the Epstein-Barr virus. *Mol. Pathol.* **53**, 262-269 (2000).

225. Weiss,L.M. Epstein-Barr virus and Hodgkin's disease. *Curr. Oncol. Rep.* **2**, 199-204 (2000).

226. Muschen,M. *et al.* Rare occurrence of classical Hodgkin's disease as a T cell lymphoma. *J. Exp. Med.* **191**, 387-394 (2000).

227. Seitz,V. *et al.* Detection of clonal T-cell receptor gamma-chain gene rearrangements in Reed-Sternberg cells of classic Hodgkin disease. *Blood* **95**, 3020-3024 (2000).

228. Schwering,I. *et al.* Loss of the B-lineage-specific gene expression program in Hodgkin and Reed-Sternberg cells of Hodgkin lymphoma. *Blood* **101**, 1505-1512 (2003).

229. Joos,S. *et al.* Classical Hodgkin lymphoma is characterized by recurrent copy number gains of the short arm of chromosome 2. *Blood* **99**, 1381-1387 (2002).

230. Weber-Matthiesen,K., Deerberg,J., Poetsch,M., Grote,W., & Schlegelberger,B. Numerical chromosome aberrations are present within the CD30+ Hodgkin and Reed-Sternberg cells in 100% of analyzed cases of Hodgkin's disease. *Blood* **86**, 1464-1468 (1995).

231. Cabannes,E., Khan,G., Aillet,F., Jarrett,R.F., & Hay,R.T. Mutations in the IkBa gene in Hodgkin's disease suggest a tumour suppressor role for IkappaBalpha. *Oncogene* **18**, 3063-3070 (1999).

232. Emmerich,F. *et al.* Overexpression of I kappa B alpha without inhibition of NF-kappaB activity and mutations in the I kappa B alpha gene in Reed-Sternberg cells. *Blood* **94**, 3129-3134 (1999).

233. Emmerich,F. *et al.* Inactivating I kappa B epsilon mutations in Hodgkin/Reed-Sternberg cells. *J. Pathol.* **201**, 413-420 (2003).

234. Jungnickel,B. *et al.* Clonal deleterious mutations in the IkappaBalpha gene in the malignant cells in Hodgkin's lymphoma. *J. Exp. Med.* **191**, 395-402 (2000).

235. Maggio,E.M., van den,B.A., de,J.D., Diepstra,A., & Poppema,S. Low frequency of FAS mutations in Reed-Sternberg cells of Hodgkin's lymphoma. *Am. J. Pathol.* **162**, 29-35 (2003).

236. Xerri,L., Carbuccia,N., Parc,P., Hassoun,J., & Birg,F. Frequent expression of FAS/APO-1 in Hodgkin's disease and anaplastic large cell lymphomas. *Histopathology* **27**, 235-241 (1995).

237. Metkar,S.S. *et al.* Expression of Fas and Fas ligand in Hodgkin's disease. *Leuk. Lymphoma* **33**, 521-530 (1999).

238. Verbeke,C.S., Wenthe,U., Grobholz,R., & Zentgraf,H. Fas ligand expression in Hodgkin lymphoma. *Am. J. Surg. Pathol.* **25**, 388-394 (2001).

239. Re,D., Hofmann,A., Wolf,J., Diehl,V., & Staratschek-Jox,A. Cultivated H-RS cells are resistant to CD95L-mediated apoptosis despite expression of wild-type CD95. *Exp. Hematol.* **28**, 348 (2000).

240. Muschen,M. *et al.* Somatic mutations of the CD95 gene in Hodgkin and Reed-Sternberg cells. *Cancer Res.* **60**, 5640-5643 (2000).

241. Dutton,A. *et al.* Expression of the cellular FLICE-inhibitory protein (c-FLIP) protects Hodgkin's lymphoma cells from autonomous Fas-mediated death. *Proc. Natl. Acad. Sci. U. S. A* **101**, 6611-6616 (2004).

242. Mathas,S. *et al.* c-FLIP mediates resistance of Hodgkin/Reed-Sternberg cells to death receptor-induced apoptosis. *J. Exp. Med.* **199**, 1041-1052 (2004).

243. Kashkar,H. *et al.* XIAP-mediated caspase inhibition in Hodgkin's lymphoma-derived B cells. *J. Exp. Med.* **198**, 341-347 (2003).

244. Kreuz,S., Siegmund,D., Scheurich,P., & Wajant,H. NF-kappaB inducers upregulate cFLIP, a cycloheximide-sensitive inhibitor of death receptor signaling. *Mol. Cell Biol.* **21**, 3964-3973 (2001).

245. Hinz,M. *et al.* Constitutive NF-kappaB maintains high expression of a characteristic gene network, including CD40, CD86, and a set of antiapoptotic genes in Hodgkin/Reed-Sternberg cells. *Blood* **97**, 2798-2807 (2001).

246. Rickinson,A.B., Yao,Q.Y., & Wallace,L.E. The Epstein-Barr virus as a model of virus-host interactions. *Br. Med. Bull.* **41**, 75-79 (1985).

247. Brousset,P. *et al.* Persistence of the same viral strain in early and late relapses of Epstein-Barr virus-associated Hodgkin's disease. *Blood* **84**, 2447-2451 (1994).

248. Kilger,E., Kieser,A., Baumann,M., & Hammerschmidt,W. Epstein-Barr virus-mediated B-cell proliferation is dependent upon latent membrane protein 1, which simulates an activated CD40 receptor. *EMBO J.* **17**, 1700-1709 (1998).

249. Caldwell,R.G., Wilson,J.B., Anderson,S.J., & Longnecker,R. Epstein-Barr virus LMP2A drives B cell development and survival in the absence of normal B cell receptor signals. *Immunity.* **9**, 405-411 (1998).

250. Casola,S. *et al.* B cell receptor signal strength determines B cell fate. *Nat. Immunol.* **5**, 317-327 (2004).

251. Vockerodt,M. *et al.* An unbalanced translocation involving chromosome 14 is the probable cause for loss of potentially functional rearranged immunoglobulin heavy chain genes in the Epstein-Barr virus-positive Hodgkin's lymphoma-derived cell line L591. *Br. J. Haematol.* **119**, 640-646 (2002).

252. Bechtel,D., Kurth,J., Unkel,C., & Kuppers,R. Transformation of BCR-deficient germinal-center B cells by EBV supports a major role of the virus in the pathogenesis of Hodgkin and posttransplantation lymphomas. *Blood* **106**, 4345-4350 (2005).

253. Chaganti,S. *et al.* Epstein-Barr virus infection in vitro can rescue germinal center B cells with inactivated immunoglobulin genes. *Blood* **106**, 4249-4252 (2005).

254. Mancao,C., Altmann,M., Jungnickel,B., & Hammerschmidt,W. Rescue of "crippled" germinal center B cells from apoptosis by Epstein-Barr virus. *Blood* **106**, 4339-4344 (2005).

255. Benharroch,D. *et al.* Measles virus: evidence of an association with Hodgkin's disease. *Br. J. Cancer* **91**, 572-579 (2004).

256. zur,H.H. & de Villiers,E.M. Virus target cell conditioning model to explain some epidemiologic characteristics of childhood leukemias and lymphomas. *Int. J. Cancer* **115**, 1-5 (2005).

257. Ryan,J.L. *et al.* Epstein-Barr virus quantitation by real-time PCR targeting multiple gene segments: a novel approach to screen for the virus in paraffin-embedded tissue and plasma. *J. Mol. Diagn.* **6**, 378-385 (2004).

258. Griffiths-Jones,S., Grocock,R.J., van Dongen,S., Bateman,A., & Enright,A.J. miRBase: microRNA sequences, targets and gene nomenclature. *Nucleic Acids Research* **34**, D140-D144 (2006).

259. Lewis,B.P., Shih,I.H., Jones-Rhoades,M.W., Bartel,D.P., & Burge,C.B. Prediction of mammalian microRNA targets. *Cell* **115**, 787-798 (2003).

260. Dennis,G., Jr. *et al.* DAVID: Database for Annotation, Visualization, and Integrated Discovery. *Genome Biol.* **4**, 3 (2003).

261. Montgomery,R.K., Mulberg,A.E., & Grand,R.J. Development of the human gastrointestinal tract: twenty years of progress. *Gastroenterology* **116**, 702-731 (1999).

262. Cummins,J.M. *et al.* The colorectal microRNAome. *Proc. Natl. Acad. Sci. U. S. A* **103**, 3687-3692 (2006).

263. Akao,Y., Nakagawa,Y., & Naoe,T. MicroRNA-143 and -145 in colon cancer. *DNA Cell Biol.* **26**, 311-320 (2007).

264. O'Connell,R.M., Taganov,K.D., Boldin,M.P., Cheng,G., & Baltimore,D. MicroRNA-155 is induced during the macrophage inflammatory response. *Proc. Natl. Acad. Sci. U. S. A* **104**, 1604-1609 (2007).

265. Matsubara,H. *et al.* Apoptosis induction by antisense oligonucleotides against miR-17-5p and miR-20a in lung cancers overexpressing miR-17-92. *Oncogene* **26**, 6099-6105 (2007).

266. Potten,C.S., Wilson,J.W., & Booth,C. Regulation and significance of apoptosis in the stem cells of the gastrointestinal epithelium. *Stem Cells* **15**, 82-93 (1997).

267. Hu,M. & Shivdasani,R.A. Overlapping gene expression in fetal mouse intestine development and human colorectal cancer. *Cancer Res.* **65**, 8715-8722 (2005).

268. He,H. *et al.* The role of microRNA genes in papillary thyroid carcinoma. *Proc. Natl. Acad. Sci. U. S. A* **102**, 19075-19080 (2005).

269. Choong,M.L., Yang,H.H., & McNiece,I. MicroRNA expression profiling during human cord blood-derived CD34 cell erythropoiesis. *Exp. Hematol.* **35**, 551-564 (2007).

270. Chui,D.T. *et al.* Classical Hodgkin lymphoma is associated with frequent gains of 17q. *Genes Chromosomes. Cancer* **38**, 126-136 (2003).

271. Kluiver,J. *et al.* Global correlation of genome and transcriptome changes in classical Hodgkin lymphoma. *Hematol. Oncol.*(2006).

272. Johansson,B. *et al.* Deletion of chromosome arm 3p in hematologic malignancies. *Leukemia* **11**, 1207-1213 (1997).

273. Sanchez-Aguilera,A. *et al.* Tumor microenvironment and mitotic checkpoint are key factors in the outcome of classic Hodgkin lymphoma. *Blood* **108**, 662-668 (2006).

274. Dave,S.S. *et al.* Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *N. Engl. J. Med.* **351**, 2159-2169 (2004).

275. Monti,S. *et al.* Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflammatory response. *Blood* **105**, 1851-1861 (2005).

276. Kuppers,R. & Brauninger,A. Reprogramming of the tumour B-cell phenotype in Hodgkin lymphoma. *Trends Immunol.* **27**, 203-205 (2006).

277. Schwering,I. *et al.* Loss of the B-lineage-specific gene expression program in Hodgkin and Reed-Sternberg cells of Hodgkin lymphoma. *Blood* **101**, 1505-1512 (2003).

278. Ushmorov,A. *et al.* Epigenetic silencing of the immunoglobulin heavy-chain gene in classical Hodgkin lymphoma-derived cell lines contributes to the loss of immunoglobulin expression. *Blood* **104**, 3326-3334 (2004).

279. Yeung,M.L. *et al.* Changes in microRNA expression profiles in HIV-1-transfected human cells. *Retrovirology.* **2**, 81 (2005).

280. Sarnow,P., Jopling,C.L., Norman,K.L., Schutz,S., & Wehner,K.A. MicroRNAs: expression, avoidance and subversion by vertebrate viruses. *Nat. Rev. Microbiol.* **4**, 651-659 (2006).

281. Pfeffer,S. & Voinnet,O. Viruses, microRNAs and cancer. *Oncogene* **25**, 6211-6219 (2006).

282. Jarrett,R.F. *et al.* Impact of tumor Epstein-Barr virus status on presenting features and outcome in age-defined subgroups of patients with classic Hodgkin lymphoma: a population-based study. *Blood* **106**, 2444-2451 (2005).

283. Yasuda,A. *et al.* Stem cell factor/c-kit receptor signaling enhances the proliferation and invasion of colorectal cancer cells through the PI3K/Akt pathway. *Digestive Diseases and Sciences* **52**, 2292-2300 (2007).

284. McDonald,S.A., Preston,S.L., Lovell,M.J., Wright,N.A., & Jankowski,J.A. Mechanisms of disease: from stem cells to colorectal cancer. *Nat. Clin. Pract. Gastroenterol. Hepatol.* **3**, 267-274 (2006).

285. Re,D., Kuppers,R., & Diehl,V. Molecular pathogenesis of Hodgkin's lymphoma. *Journal of Clinical Oncology* **23**, 6379-6386 (2005).

286. Kuppers,R. Pathogenesis of Hodgkin lymphoma. *European Journal of Clinical Investigation* **37**, 57 (2007).

287. Bach,S.P., Renehan,A.G., & Potten,C.S. Stem cells: the intestinal stem cell as a paradigm. *Carcinogenesis* **21**, 469-476 (2000).

288. Wong,W.M., Garcia,S.B., & Wright,N.A. Origins and morphogenesis of colorectal neoplasms. *APMIS* **107**, 535-544 (1999).

289. Fearon,E.R., Hamilton,S.R., & Vogelstein,B. Clonal analysis of human colorectal tumors. *Science* **238**, 193-197 (1987).

290. Renehan,A.G., Bach,S.P., & Potten,C.S. The relevance of apoptosis for cellular homeostasis and tumorigenesis in the intestine. *Can. J. Gastroenterol.* **15**, 166-176 (2001).

291. Knuutila,S. *et al.* DNA copy number amplifications in human neoplasms: review of comparative genomic hybridization studies. *Am. J. Pathol.* **152**, 1107-1123 (1998).

292. Ota,A. *et al.* Identification and characterization of a novel gene, C13orf25, as a target for 13q31-q32 amplification in malignant lymphoma. *Cancer Res.* **64**, 3087-3095 (2004).

293. Skinnider,B.F. & Mak,T.W. The role of cytokines in classical Hodgkin lymphoma. *Blood* **99**, 4283-4297 (2002).

294. Maggio,E. *et al.* Chemokines, cytokines and their receptors in Hodgkin's lymphoma cell lines and tissues. *Ann. Oncol.* **13 Suppl 1**, 52-56 (2002).

295. Loffler,D. *et al.* Interleukin-6 dependent survival of multiple myeloma cells involves the Stat3-mediated induction of microRNA-21 through a highly conserved enhancer. *Blood* **110**, 1330-1333 (2007).

296. Esquela-Kerscher,A. & Slack,F.J. Oncomirs - microRNAs with a role in cancer. *Nat. Rev. Cancer* **6**, 259-269 (2006).

297. He,L. *et al.* A microRNA polycistron as a potential human oncogene. *Nature* **435**, 828-833 (2005).