

DAFTAR PUSTAKA

- Almas, I., Afzal, S., Idrees, M., Ashraf, M.U., Amin, I., Shahid, M., Zahid, K., & Zahid, S., 2017, Role of circulatory microRNAs in the pathogenesis of hepatitis C virus. *Virusdisease*, 28(4):360-367. <https://doi.org/10.1007/s13337-017-0407-3>.
- Ameres, S.L., & Zamore, P.D., 2013, Diversifying microRNA sequence and function, *Nat Rev Mol Cell Biol*, 14(8):475–88. <https://doi.org/10.1038/nrm3611>.
- Anwar, S.L., & Lehmann, U., 2015, MicroRNAs: Emerging Novel Clinical Biomarkers for Hepatocellular Carcinomas, *J Clin Med*, 4(8):1631-1650. <https://doi.org/10.3390/jcm4081631>.
- Attwa, M.H., & El-Etreby, S.A., 2015, Guide for diagnosis and treatment of hepatocellular carcinoma, *World J Hepatol*, 7: 1632-1651. <https://doi.org/10.4254/wjh.v7.i12.1632>.
- Bai, X., Liu, Z., Shao, X., Wang, D., Dong, E., & Wang, Y., 2019, The heterogeneity of plasma miRNA profiles in hepatocellular carcinoma patients and the exploration of diagnostic circulating miRNAs for hepatocellular carcinoma, *PLoS ONE*, 14(2):e0211581. <https://doi.org/10.1371/journal.pone.0211581>.
- Baranova, A., Lal, P., Bireddinc, A., & Younossi Z.M., 2011, Non-invasive markers for hepatic fibrosis, *BMC Gastroenterol*, 11(1). <https://doi.org/10.1186/1471-230X-11-91>.
- Benes, V., & Castoldi, M., 2010, Expression profiling of microRNA using real-time quantitative PCR, how to use it and what is available. *Methods*, 50(4):244-249. <https://doi.org/10.1016/j.ymeth.2010.01.026>.
- Bhan, I., Haber, D.A., Chung, R.T., & Ting, D.T., 2019, Liquid Biopsy in Hepatocellular Carcinoma, In: Hoshida Y, editor. *Hepatocellular Carcinoma: Translational Precision Medicine Approaches*, Cham (CH): Humana Press; 2019. Chap 7. https://doi.org/10.1007/978-3-030-21540-8_7.
- Bishayee, A., 2014, The role of inflammation and liver cancer, *Adv Exp Med Biol*, 816:401-35. https://doi.org/10.1007/978-3-0348-0837-8_16.
- Bodzin, A.S., & Busuttil, R.W., 2015, Hepatocellular carcinoma: Advances in diagnosis, management, and long term outcome, *World J Hepatol*, 7: 1157-1167. <https://doi.org/10.4254/wjh.v7.i9.1157>.
- Boldrini, L., Giordano, M., Niccoli, C., Melfi, F., Lucchi, M., Mussi, A., & Fontanini, G., 2017, Role of microRNA-33a in regulating the expression of PD-1 in lung adenocarcinoma, *Cancer Cell Int*, 17(1), <https://doi.org/10.1186/s12935-017-0474-y>.
- Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., & Jemal, A., 2018, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *CA Cancer J Clin*, 68(6):394-424. <https://doi.org/10.3322/caac.21492>.

- Bruix J, Sherman M; 2011, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update, *Hepatology*, 53(3):1020-2. <https://doi.org/10.1002/hep.24199>.
- Burrell, R.A., McGranahan, N., Bartek, J., & Swanton, C., 2013, The causes and consequences of genetic heterogeneity in cancer evolution, *Nature*, 338–345. <https://doi.org/10.1038/nature12625>.
- Chang, R.M., Xu, J.F., Fang, F., Yang, H., & Yang, L.Y., 2016, MicroRNA-130b promotes proliferation and EMT-induced metastasis via PTEN/p-AKT/HIF-1 α signaling, *Tumour Biol*, 37(8):10609–10619. <https://doi.org/10.1007/s13277-016-4919-z>.
- Chang, Y.Y., Kuo, W.H., Hung, J.H., Lee, C.Y., Lee, Y.H., Chang, Y.C., Lin, W.C., Shen, C.Y., Huang, C.S., Hsieh, F.J., Lai, L.C., Tsai, M.H., Chang, K.J., & Chuang, E.Y., 2015, Deregulated microRNAs in triple-negative breast cancer revealed by deep sequencing, *Mol Cancer*, 14:36. <https://doi.org/10.1186/s12943-015-0301-9>.
- Chen, G., Wang, J., & Cui Q., 2013, Could circulating miRNAs contribute to cancer therapy? *Trends Mol Med*, 19:71–73. <https://doi.org/10.1016/j.molmed.2012.10.006>.
- Chen, J., Hu, C., & Pan, P., 2017, Extracellular Vesicle MicroRNA Transfer in Lung Diseases, *Front Physiol*, 8:1028. <https://doi.org/10.3389/fphys.2017.01028>.
- Cheng, B., Ding, F., Huang, C.Y., Xiao, H., Fei, F.Y., and Li, J., 2019, Role of miR-16-5p in the proliferation and metastasis of hepatocellular carcinoma, *Eur Rev Med Pharmacol Sci*, 23(1):137-145. https://doi.org/10.26355/eurrev_201901_16757.
- Cheng, G., 2015, Circulating miRNAs: roles in cancer diagnosis, prognosis and therapy, *Adv Drug Deliv Rev*, 81:75-93. <https://doi.org/10.1016/j.addr.2014.09.001>.
- Colombo, M., Moita, C., Van Niel, G., Kowal, J., Vigneron, J., Benaroch, P., Manel, N., Moita, L.F., Théry, C., Raposo, G., 2013, Analysis of ESCRT functions in exosome biogenesis, composition and secretion highlights the heterogeneity of extracellular vesicles, *J Cell Sci*, 126(Pt 24):5553-65. <https://doi.org/10.1242/jcs.128868>.
- Cortez, M.A., Bueso-Ramos, C., Ferdin, J., Lopez-Berestein, G., Sood, A.K., & Calin, G.A., 2011, MicroRNAs in body fluids- the mix of hormones and biomarkers, *Nat Rev Clin Oncol*, 8:467–477. <https://doi.org/10.1038/nrclinonc.2011.76>.
- Dagogo-Jack, I., & Shaw, A.T., 2018, Tumour heterogeneity and resistance to cancer therapies, *Nat Rev Clin Oncol*, 15(2):81-94. <https://doi.org/10.1038/nrclinonc.2017.166>.
- Dai, J., Su, Y., Zhong, S., Cong, L., Liu, B., Yang, J., Tao, Y., He, Z., Chen, C., & Jiang, Y., 2020, Exosomes: key players in cancer and potential therapeutic strategy, *Sig Transduct Target Ther*, 5(1):145, <https://doi.org/10.1038/s41392-020-00261-0>.

- Dufour, J.F., Greten, T.F., Raymond, E., et al., 2012, Clinical practice guidelines EASL – EORTC clinical practice guidelines: Management of hepatocellular carcinoma European Organisation for Research and Treatment of Cancer, *J Hepatol*, 56(4):908-43. <https://doi.org/10.1016/j.jhep.2011.12.001>.
- Fabregat, I., Moreno-Càceres, J., Sánchez, A., Dooley, S., Dewidar, B., Giannelli, G., Ten Dijke, P., 2016, IT-LIVER Consortium. TGF- β signalling and liver disease. *FEBS J*. 283(12):2219-32. <https://doi.org/10.1111/febs.13665>.
- Faivre, S., Bouattour, M., & Raymond, E., 2011, Novel molecular therapies in hepatocellular carcinoma, *Liver Int*. 31(Suppl 1):151-160. <https://doi.org/10.1111/j.1478-3231.2010.02395.x>.
- Fedele, C., Tothill, R.W., & McArthur, G.A., 2014, Navigating the challenge of tumor heterogeneity in cancer therapy, *Cancer Discov*, 4:146–148. <https://doi.org/10.1158/2159-8290.CD-13-1042>.
- Ferlay, J., Soerjomataram, I., Dikshit, R., et al., 2015, Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012, *Int J Cancer*, 136(5):E359-E386. <https://doi.org/10.1002/ijc.29210>.
- Fornier, A., Reig, M., & Bruix, J., 2018, Hepatocellular carcinoma. *Lancet*. 391(10127):1301-1314. [https://doi.org/10.1016/S0140-6736\(18\)30010-2](https://doi.org/10.1016/S0140-6736(18)30010-2).
- Friedman, S.L., 2008, Mechanisms of hepatic fibrogenesis, *Gastroenterology*, 134(6):1655-1669. <https://doi.org/10.1053/j.gastro.2008.03.003>.
- Gadkar, V.Y.J., & Filion, M., 2014, New Developments in Quantitative Real-time Polymerase Chain Reaction Technology, *Curr Issues Mol Biol*, 16:1–6. <http://dx.doi.org/10.21775/cimb.016.001>.
- Gerlinger, M., Horswell, S., Larkin, J., Rowan, A.J., Salm, M.P., & Varela, I., 2014, Genomic architecture and evolution of clear cell renal cell carcinomas defined by multiregion sequencing, *Nat Genet*, 46:225–233. <https://doi.org/10.1038/ng.2891>.
- Gilad, S., Meiri, E., Yogev, Y., Benjamin, S., Lebanony, D., & Yerushalmi N., 2008, Serum MicroRNAs Are Promising Novel Biomarkers, *PLoS One*, 3. Artn E3148. <https://doi.org/10.1371/Journal.Pone.0003148>.
- GLOBOCAN, 2018, Liver, The Global Cancer Observatory International Agency for Research on Cancer, *World Health Organization*. <http://gco.iarc.fr/today>.
- Gong, X.C., Xu, Y.Q., Jiang, Y., Guan, H., & Liu, H.L., 2016, Onco-microRNA miR-130b promoting cell growth in children APL by targeting PTEN. *Asian Pac J Trop Med*, 9(3):265-8. <https://doi.org/10.1016/j.apjtm.2016.01.024>.
- Guicciardi, M.E., & Gores, G.J., 2010, Apoptosis as a mechanism for liver disease progression, *Semin Liver Dis*, 30(4):402-410. <https://doi.org/10.1055/s-0030-1267540>.
- Hanahan, D., & Weinberg, R.A., 2011, Hallmarks of cancer: the next generation, *Cell*, 144(5):646-674. <https://doi.org/10.1016/j.cell.2011.02.013>.

- Harris, P.S., Hansen, R.M., Gray, M.E., Massoud, O.I., McGuire, B.M., & Shoreibah, M.G., 2019, Hepatocellular carcinoma surveillance: An evidence-based approach. *World J Gastroenterol*, 25(13):1550-1559. <https://doi.org/10.3748/wjg.v25.i13.1550>.
- Hayes, C.N., & Chayama, K., 2016, MicroRNAs as Biomarkers for Liver Disease and Hepatocellular Carcinoma, *Int J Mol Sci*, 17:280. <https://doi.org/10.3390/ijms17030280>.
- Heldin, C.H., Landström, M., & Moustakas, A., 2009, Mechanism of TGF- β signaling to growth arrest, apoptosis, and epithelial–mesenchymal transition, *Current Opinion in Cell Biology*, 21(2):166–176. <https://doi.org/10.1016/j.ceb.2009.01.021>.
- Hessvik, N.P., & Llorente, A., 2018, Current knowledge on exosome biogenesis and release, *Cell Mol. Life Sci*, 75(2):193-208, <https://doi.org/10.1007/s00018-017-2595-9>.
- Hoshida, Y., Fuchs, B.C., Bardeesy, N., Baumert, T.F., & Chung, R.T., 2014, Pathogenesis and prevention of hepatitis C virus-induced hepatocellular carcinoma, *JHepatol*. 61(1 Suppl):S79-S90. <https://doi.org/10.1016/j.jhep.2014.07.010>.
- Huang, J.L., Zheng, L., Hu, Y.W., & Wang, Q., 2014, Characteristics of long non-coding RNA and its relation to hepatocellular carcinoma. *Carcinogenesis*, 35(3):507-14. <https://doi.org/10.1093/carcin/bgt405>.
- Hurley, J.H., & Hanson, P.I., 2010, Membrane budding and scission by the ESCRT machinery: it's all in the neck, *Nat Rev Mol cell Biol*, 11(8):556-66. <https://doi.org/10.1038/nrm2937>.
- Ibrahim, A., & Marban, E., 2016, Exosomes: fundamental biology and roles in cardiovascular physiology, *Annu Rev. Physiol*, 78:67-83. <https://doi.org/10.1146/annurev-physiol-021115-104929>.
- Ikushima, H., Miyazono, K., 2010, TGFbeta signalling: a complex web in cancer progression, *Nat Rev Cancer*, 10(6):415-24. <https://doi.org/10.1038/nrc2853>.
- Jemal, A., Bray, F., Center, M.M., Ferlay, J., Ward, E., & Forman, D., 2011, Global cancer statistics, *CA Cancer J Clin*, 61(2):69-90. <https://doi.org/10.3322/caac.20107>.
- Ji, F., Zhang, Z., & Zhang, Y., 2018, Low expression of c-Myc protein predicts poor outcomes in patients with hepatocellular carcinoma after resection *BMC Cancer*, 18:460. <https://doi.org/10.1186/s12885-018-4379-5>.
- Jie, P.I., Kholili, U., & Kurniasari, N., 2016, Karakteristik Penderita Karsinoma Hepatoseluler di RSUD Dokter Soetomo Tahun 2014-2016. *Universitas Airlangga*.<http://repository.unair.ac.id/75973/1/PRISCILLIA%20abstrak.pdf>.
- Jung, C.J., Iyengar, S., Blahnik, K.R., Jiang, J.X., Tahimic, C., Torok, N.J., de vere White, R.W., Farnham, P.J., Zern, M., 2012, Human ESC self-renewal promoting microRNAs induce epithelial-mesenchymal transition in hepatocytes by controlling the PTEN and TGF β tumor suppressor

- signaling pathways. *Mol Cancer Res.* 10(7):979-91. <https://doi.org/10.1158/1541-7786.MCR-11-0421>.
- Kalluri, R., & LeBleu, V.S., 2020, The biology, function, and biomedical applications of exosomes, *Science*, 367(6478):eaau6977. <https://doi.org/10.1126/science.aau6977>.
- Kerr, T.A., Korenblat, K.M., & Davidson, N.O., 2011, MicroRNAs and liver disease, *Transl Res*, 157(4):241-252. <https://doi.org/10.1016/j.trsl.2011.01.008>.
- Kulik, L. & El-Serag, H.B., 2019, Epidemiology and Management of Hepatocellular Carcinoma, *Gastroenterology*, 156(2):477–91. <https://doi.org/10.1053/j.gastro.2018.08.065>.
- Lässer, C., 2012, Exosomal RNA as biomarkers and the therapeutic potential of exosome vectors, *Expert Opin Biol Ther*, 12 Suppl 1:S189-97. <https://doi.org/10.1517/14712598.2012.680018>.
- Lemoinne, S., Thabut, D., Housset, C., Moreau, R., Valla, D., Boulanger, C.M., & Rautou, P.E, 2014, The emerging roles of microvesicles in liver diseases, *Nat Rev Gastroenterol Hepatol*, 11(6):350–361. <https://doi.org/10.1038/nrgastro.2014.7>.
- Li, D., Liu, X., Lin, L., Hou, J., Li, N., & Wang C., 2011, MicroRNA-99a inhibits hepatocellular carcinoma growth and correlates with prognosis of patients with hepatocellular carcinoma, *J Biol Chem*, 286:36677–36685. <https://doi.org/10.1074/jbc.M111.270561>.
- Li, H., Yang, R., Fan, X., et al., 2012, MicroRNA array analysis of microRNAs related to systemic scleroderma, *Rheumatol Int*, 32(2):307-313. <https://doi.org/10.1007/s00296-010-1615-y>.
- Lin, C.P., Liu, C.R., Lee, C.N., Chan, T.S., & Liu, H.E., 2010, Targeting c-Myc as a novel approach for hepatocellular carcinoma. *World journal of hepatology*, 2(1):16–20. <https://doi.org/10.4254/wjh.v2.i1.16>
- Liu, A.M., Yao, T.J., Wang, W., Wong, K.F., Lee, N.P., Fan, S.T., Poon, R.T., Gao, C., & Luk, J.M., 2012, Circulating miR-15b and miR-130b in serum as potential markers for detecting hepatocellular carcinoma: a retrospective cohort study, *BMJ Open*, 2(2):e000825. <https://doi.org/10.1136/bmjopen-2012-000825>.
- Liu, Z., Wei, X., Chen, T., Huang, C., Liu, H., & Wang, Y., 2017, Characterization of fibrosis changes in chronic hepatitis C patients after virological cure: A systematic review with meta-analysis, *J Gastroenterol Hepatol*, 32(3):548-557. <https://doi.org/10.1111/jgh.13500>
- Livak, K.J., & Schmittgen, T.D., 2001, Analysis of relative gene expression data using real-time quantitative PCR and the 2⁻(-Delta Delta C(T)) Method, *Methods*, 25(4):402-408. <https://doi.org/10.1006/meth.2001.1262>
- Loosen, S.H., Schueller, F., Trautwein, C., Roy, S., & Roderburg, C., 2017, Role of circulating microRNAs in liver diseases, *World J Hepatol*, 9(12):586–594. <https://doi.org/10.4254/wjh.v9.i12.586>.
- Ludwig, N., Nourkani-Tutdibi, N., Backes, C., Lenhof, H. P., Graf, N., Keller, A., & Meese, E., 2015, Circulating serum miRNAs as potential

- biomarkers for neuroblastoma. *Pediatric Blood & Cancer*, 62:1360–1367. <https://doi.org/10.1002/pbc.25481>.
- Ma, S., Tang, K.H., Chan, Y.P., Lee, T.K., Kwan, P.S., Castilho, A., Ng, I., Man, K., Wong, N., To, K.F., Zheng, B.J., Lai, P.B., Lo, C.M., Chan, K.W., & Guan, X.Y., 2010, miR-130b Promotes CD133(+) liver tumor-initiating cell growth and self-renewal via tumor protein 53-induced nuclear protein 1, *Cell Stem Cell*, 7(6):694-707. <https://doi.org/10.1016/j.stem.2010.11.010>.
- Marusyk, A., & Polyak, K., 2010, Tumor heterogeneity: causes and consequences, *Biochim Biophys Acta*, 1805(1):105-117. <https://doi.org/10.1016/j.bbcan.2009.11.002>.
- Mazzoccoli, G., Tarquini, R., Valoriani, A., Oben, J., Vinciguerra, M., & Marra, F., 2016, Management strategies for hepatocellular carcinoma: old certainties and new realities, *Clin Exp Med*, 16(3):243-256. <https://doi.org/10.1007/s10238-015-0368-z>.
- McGivern, D.R., & Lemon, S.M., 2011, Virus-specific mechanisms of carcinogenesis in hepatitis C virus associated liver cancer, *Oncogene*, 30(17):1969-1983. <https://doi.org/10.1038/onc.2010.594>.
- McGranahan, N., & Swanton, C., 2017, Clonal Heterogeneity and Tumor Evolution: Past, Present, and the Future, *Cell*, 613–628. <https://doi.org/10.1016/j.cell.2017.01.018>.
- Mimeault, M. & Batra, S.K., 2014, Molecular biomarkers of cancer stem/progenitor cells associated with progression, metastases, and treatment resistance of aggressive cancers, *Cancer Epidemiol Biomark Prev*, 23(2):234-54. <https://doi.org/10.1158/1055-9965.EPI-13-0785>.
- Mitchell, P.S., Parkin, R.K., Kroh, E.M., Fritz, B.R., Wyman, S.K., Pogosova-Agadjanyan, E.L., Peterson, A., Noteboom, J., O'Briant, K.C., Allen, A., Lin, D.W., Urban, N., Drescher, C.W., Knudsen, B.S., Stirewalt, D.L., Gentleman, R., Vessella, R.L., Nelson, P.S., Martin, D.B., & Tewari, M., 2008, Circulating microRNAs as stable blood-based markers for cancer detection, *Proc Natl Acad Sci U S A*, 105(30):10513-8. <https://doi.org/10.1073/pnas.0804549105>.
- Morris, S.M., Baek, J.Y., Koszarek, A., Kanngurn, S., Knoblaugh, S.E., Grady, W.M., 2012, Transforming growth factor-beta signaling promotes hepatocarcinogenesis induced by p53 loss, *Hepatology*, 55(1):121-31. <https://doi.org/10.1002/hep.24653>.
- Nadhim, M.R.P., Suharti, C., Hardian, 2016, Distribusi Geografis dan Tingkat Keparahan Pasien Karsinoma Hepatoseluler Etiologi Virus Hepatitis B di RS. Dr Kariadi, *Jurnal Kedokteran Diponegoro*, 5:4. <https://garuda.ristekbrin.go.id/documents/detail/1421595>.
- Navin, P.J., & Venkatesh, S.K., 2019, Hepatocellular Carcinoma: State of the Art Imaging and Recent Advances, *J Clin Transl Hepatol*. 7(1):72-85. <https://doi.org/10.14218/JCTH.2018.00032>.
- Petrovčíková, E., Vičíková, K., & Leksa, V., 2018, Extracellular vesicles-biogenesis, composition, function, uptake and therapeutic

- applications, *Biologia*, 73(4): 437-448. <https://doi.org/10.2478/s11756-018-0047-0>.
- Piñero, F., Dirchwolf, M., & Pessôa, M.G., 2020, Biomarkers in Hepatocellular Carcinoma: Diagnosis, Prognosis and Treatment Response Assessment, *Cells*, 9(6): 1370. <https://doi.org/10.3390/cells9061370>
- Pisitkun, T., Shen, R.F., & Knepper, M.A., 2004, Identification and proteomic profiling of exosomes in human urine, *Proc Natl Acad USA*, 101(36), 13368–13373. <https://doi.org/10.1073/pnas.0403453101>.
- Pok, S., Barn, V.A., Wong, H.J., Blackburn, A.C., Board, P., Farrell, G.C., & Teoh, N.C., 2016, Testosterone regulation of cyclin E kinase: A key factor in determining gender differences in hepatocarcinogenesis. *J Gastroenterol Hepatol*. 31(6):1210-9. <https://doi.org/10.1111/jgh.13232>.
- Pratama, M.Y., Cavalletto, L., Tiribelli, C. *et al.*, 2020, Selection and validation of miR-1280 as a suitable endogenous normalizer for qRT-PCR Analysis of serum microRNA expression in Hepatocellular Carcinoma. *Sci Rep*, 10, 3128. <https://doi.org/10.1038/s41598-020-59682-0>.
- Puhka, M., Takatalo, M., Nordberg, M.E., Valkonen, S., Nandania, J., Aatonen, M., Yliperttula, M., Laitinen, S., Velagapudi, V., Mirtti, T., Kallioniemi, O., Rannikko, A., Siljander, P.R., Af Hällström, T.M., 2017, Metabolomic Profiling of Extracellular Vesicles and Alternative Normalization Methods Reveal Enriched Metabolites and Strategies to Study Prostate Cancer-Related Changes, *Theranostics*, 7(16):3824-3841. <https://doi.org/10.7150/thno.19890>.
- Qi, P., Cheng, S., Wang, H., Li, H., Chen, Y., & Gao, C., 2011, Serum microRNAs as biomarkers for hepatocellular carcinoma in Chinese patients with chronic hepatitis B virus infection, *PloS One*, 6(12):e28486. <https://doi.org/10.1371/journal.pone.0028486>.
- Ramakrishna, G., Rastogi, A., Trehanpati, N., Sen, B., Khosla, R., & Sarin, S.K., 2013, From cirrhosis to hepatocellular carcinoma: new molecular insights on inflammation and cellular senescence, *Liver Cancer*, 2(3-4):367-83. <https://doi.org/10.1159/000343852>.
- Ronot, M., Purcell, Y., & Vilgrain, V., 2019, Hepatocellular Carcinoma: Current Imaging Modalities for Diagnosis and Prognosis, *Dig Dis Sci*, 64(4):934-950. <https://doi.org/10.1007/s10620-019-05547-0>.
- Ruivo, C. F., Adem, B., Silva, M. & Melo, S. A., 2017, The biology of cancer exosomes: insights and new perspectives, *Cancer Res*, 77(23):6480-6488. <https://doi.org/10.1158/0008-5472.CAN-17-0994>.
- Rupaimoole, R., & Slack, F.J., 2017, MicroRNA therapeutics: towards a new era for the management of cancer and other diseases, *Nat Rev Drug Discov*, 16(3):203-222. <https://doi.org/10.1038/nrd.2016.246>.
- Sadri, N.J., Bokharaei-Salim, F., Salmaninejad, A., Nesaei, A., Mohajeri, F., & Moshtazan, A., 2019, microRNAs: Key players in virus-associated hepatocellular carcinoma, *J Cell Physiol*, 234(8):12188–225. <https://doi.org/10.1002/jcp.27956>.

- Schey, K.L., Luther, J.M., & Rose, K.L., 2015, Proteomics characterization of exosome cargo, *Methods*, 87:75-82. <https://doi.org/10.1016/j.ymeth.2015.03.018>
- Schoneberg, J., Lee, I.H., Iwasa, J.H., & Hurley, J.H., 2017, Reverse-topology membrane scission by the ESCRT proteins, *Nat Rev Mol cell Biol*, 18(1):5-17. <https://doi.org/10.1038/nrm.2016.121>.
- Schwarzenbach, H., & Gahan, P.B., 2019, MicroRNA Shuttle from Cell-To-Cell by Exosomes and Its Impact in Cancer, *Noncoding RNA*, 5(1):28. <https://doi.org/10.3390/ncrna5010028>.
- Sharova, E., Grassi, A., Marcer, A., Ruggero, K., Pinto, F., Bassi, P., & Ciminale, V., 2016, A circulating miRNA assay as a first-line test for prostate cancer screening. *British Journal of Cancer*, 114:1362–1366. <https://doi.org/10.1038/bjc.2016.151>.
- Shen, S., Lin, Y., Yuan, X., Shen, L., Chen, J., Chen, L., Qin, L., & Shen, B., 2016, Biomarker MicroRNAs for Diagnosis, Prognosis and Treatment of Hepatocellular Carcinoma: A Functional Survey and Comparison, *Sci Rep*. 6:38311. <https://doi.org/10.1038/srep38311>.
- Sia, D., Villanueva, A., Friedman, S.L., & Llovet, J.M., 2017, Liver Cancer Cell of Origin, Molecular Class, and Effects on Patient Prognosis, *Gastroenterology*, 152(4):745-761. <https://doi.org/10.1053/j.gastro.2016.11.048>.
- Skalsky, R.L., & Cullen, B.R., 2010, Viruses, microRNAs, and host interactions. *Annu Rev Microbiol*, 64:123–41. <https://doi.org/10.1146/annurev.micro.112408.134243>.
- Skotland, T., Sandvig, K., & Llorente, A., 2017, Lipids in exosomes: current knowledge and the way forward, *Prog lipid Res*, 66:30-41. <https://doi.org/10.1016/j.plipres.2017.03.001>.
- Stasi, C., & Milani, S., 2017, Evolving strategies for liver fibrosis staging: Non-invasive assessment, *World J Gastroenterol*, 23(2):191–196. <https://doi.org/10.3748/wjg.v23.i2.191>.
- Subra, C., Grand, D., Laulagnier, K., Stella, A., Lambeau, G., Paillasse, M., De Medina, P., Monsarrat, B., Perret, B., Silvente-Poirot, S., Poirot, M., Record, M., 2010, Exosomes account for vesicle-mediated transcellular transport of activatable phospholipases and prostaglandins, *J Lipid Res*, 51(8):2105-20. <https://doi.org/10.1194/jlr.M003657>.
- Suceveanu, A., Mazilu, L., Gheorghe, A., Stoian, A.P., Voinea, F., & Suceveanu A., 2018, Metabolic Risk Factors in Hepatocellular Carcinoma, *IntechOpen*, 97:111. <http://doi.org/10.5772/intechopen.80527>.
- Suetsugu, A., Honma, K., Saji, S., Moriwaki, H., Ochiya, T., Hoffman, R.M., 2013, Imaging exosome transfer from breast cancer cells to stroma at metastatic sites in orthotopic nude-mouse models, *Adv Drug Deliv Rev*, 65(3):383-390. <https://doi.org/10.1016/j.addr.2012.08.007>.
- Suva, M.A., 2014, A Brief Review on Liver Cirrhosis: Epidemiology, Etiology, Pathophysiology, Symptoms, Diagnosis and Its Management, *Molecular Pharmacology*. 2.

- Tachibana, C., 2015, Transcriptomics today: Microarrays, RNA-seq, and more. *Science*, 349:544-546. <https://doi.org/10.1126/science.349.6247.544>.
- Tai, Y.L., Chen, K.C., Hsieh, J.T., & Shen, T.L., 2018, Exosomes in cancer development and clinical applications, *Cancer Sci.*, 109(8):2364-2374, <https://doi.org/10.1111/cas.13697>
- Tao, J., Jiang, L., & Chen, X., 2018, Roles of microRNA in liver cancer, *Liver Res*, 2(2):61-72. <https://doi.org/10.1016/j.livres.2018.06.002>.
- Thorgeirsson, S., & Grisham, J., 2002, Molecular pathogenesis of human hepatocellular carcinoma, *Nat Genet*, 31:339-346. <https://doi.org/10.1038/ng0802-339>.
- Thulin, P., Rafter, I., Stockling, K., Tomkiewicz, C., Norjavaara, E., Aggerbeck, M., Hellmold, H., Ehrenborg, E., Andersson, U., Cotgreave, I., & Glinghammar, B., 2008, PPARalpha regulates the hepatotoxic biomarker alanine aminotransferase (ALT1) gene expression in human hepatocytes. *Toxicol Appl Pharmacol*, 231(1):1-9. <https://doi.org/10.1016/j.taap.2008.03.007>.
- Tian, X., Shen, H., Li, Z., Wang, T., & Wang, S., 2019, Tumor-derived exosomes, myeloid-derived suppressor cells, and tumor microenvironment, *J Hemato Oncol*, 12(1):84. <https://doi.org/10.1186/s13045-019-0772-z>.
- Troester, M.A., Sun, X., Allott, E.H., et al., 2018, Racial Differences in PAM50 Subtypes in the Carolina Breast Cancer Study, *J Natl Cancer Inst*, 110(2):176-182. <http://doi.org/10.1093/jnci/djx135>.
- Tsochatzis, E.A., Gurusamy, K.S., Ntaoula, S., Cholongitas, E., Davidson, B.R., & Burroughs, A.K., 2011, Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy, *J Hepatol*, 5(4):650-659. <https://doi.org/10.1016/j.jhep.2010.07.033>.
- Tu, K., Zheng, X., Dou, C., Li, C., Yang, W., Yao, Y., Liu, Q., 2014, MicroRNA-130b promotes cell aggressiveness by inhibiting peroxisome proliferator-activated receptor gamma in human hepatocellular carcinoma, *Int J Mol Sci*, 15(11):20486-99. <https://doi.org/10.3390/ijms151120486>
- Turchinovich, A., Weiz, L., Langheinz, A., & Burwinkel, B., 2011, Characterization of extracellular circulating microRNA, *Nucleic Acids Res*, 39(16):7223-7233. <https://doi.org/10.1093/nar/gkr254>.
- Valadi, H., Ekström, K., Bossios, A., Sjöstrand, M., Lee, J.J., & Lötvall, J.O., 2007, Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells, *Nat Cell Biol*, 9(6): 654-659. <https://doi.org/10.1038/ncb1596>.
- Van den Boorn, J.G., Dassler, J., Coch, C., Schlee, M., & Hartmann, G., 2013, Exosomes as nucleic acid nanocarriers, *Adv Drug Deliv Rev*, 65(3):331-5. <https://doi.org/10.1016/j.addr.2012.06.011>.
- Veldman-Jones, M.H., Brant, R., & Rooney, C., 2015, Evaluating Robustness and Sensitivity of the NanoString Technologies nCounter Platform to Enable Multiplexed Gene Expression Analysis of Clinical Samples, *Cancer Res*, 75:2587-2593. <https://doi.org/10.1158/0008-5472.CAN-15-0262>.
- Venook, A.P., Papandreou, C., Furuse, J., & de Guevara, L.L., 2010, The incidence and epidemiology of hepatocellular carcinoma: a global and

- regional perspective. *Oncologist*, 15(Suppl 4):5-13. <https://doi.org/10.1634/theoncologist.2010-S4-05>.
- Vieira, A.F., & Schmitt, F., 2018, An Update on Breast Cancer Multigene Prognostic Tests-Emergent Clinical Biomarkers, *Front. Med*, 5:248. <https://doi.org/10.3389/fmed.2018.00248>.
- Villanueva, A., & Luedde, T., 2016, The transition from inflammation to cancer in the liver, *Clin Liver Dis*, 8(4):89-93. <https://doi.org/10.1002/cld.578>.
- Vlachos, I.S., Zagganas, K., Paraskevopoulou, M.D., Georgakilas, G., Karagkouni, D., Vergoulis, T., Dalamagas, T., & Hatzigeorgiou, A.G., 2015, DIANA-miRPath v3.0: deciphering microRNA function with experimental support, *Nucleic acids research*, 43(W1):W460–W466. <https://doi.org/10.1093/nar/gkv403>
- Wakefield, L.M., & Hill, C.S., 2013, Beyond TGFβ: roles of other TGFβ superfamily members in cancer. *Nat Rev Cancer*, 13(5):328–341. <https://doi.org/10.1038/nrc3500>.
- Wallden, B., Storhoff, J., Nielsen, T., et al., 2015, Development and verification of the PAM50-based Prosigna breast cancer gene signature assay, *BMC Med Genomics*, 8:54. <https://doi.org/10.1186/s12920-015-0129-6>.
- Wang, G., Chen, H.W., Oktay, Y., Zhang, J., Allen, E.L., Smith, G.M., Fan, K.C., Hong, J.S., French, S.W., McCaffery, J.M., Lightowers, R.N., Morse III, H.C., Koehler, C.M., & Teitell, M.A., 2010, PNPase regulates RNA import into mitochondria, *Cell*, 142(3):456-67. <https://doi.org/10.1016/j.cell.2010.06.035>.
- Winter, J., Jung, S., Keller, S., et al., 2009, Many roads to maturity: microRNA biogenesis pathways and their regulation, *Nat Cell Biol*, 11:228–234. <https://doi.org/10.1038/ncb0309-228>.
- Wong, C., Tsang, F., & Ng, I., 2018, Non-coding RNAs in hepatocellular carcinoma: molecular functions and pathological implications, *Nat Rev Gastroenterol Hepatol*, 15:137–151. <https://doi.org/10.1038/nrgastro.2017.169>.
- Wong, R.J., Ahmed, A., & Gish, R.G., 2015, Elevated alpha-fetoprotein: differential diagnosis - hepatocellular carcinoma and other disorders, *Clin Liver Dis* 19(2):309-23. <https://doi.org/10.1016/j.cld.2015.01.005>.
- Wortzel, I., Dror, S., Kenific, C.M., & Lyden, D., 2019, Exosome-mediated metastasis: communication from a distance, *Dev Cell*, 49(3):347-360. <https://doi.org/10.1016/j.devcel.2019.04.011>.
- Xie, K., Chen, C.H., Tsai, S.P., Lu, P.J., Wu, H., Zeng, Y., Ye, .Y, Tu, H., Wen, C., Huang, M., Zhang, Y., Lee, J.H., Tsai, M.K., Wen, C.P., & Wu, X., 2019. Loss of Life Expectancy by 10 Years or More From Elevated Aspartate Aminotransferase: Finding Aspartate Aminotransferase a Better Mortality Predictor for All-Cause and Liver-Related than Alanine Aminotransferase, *Am J Gastroenterol*, 114(9):1478-1487. <https://doi.org/10.14309/ajg.0000000000000332>.
- Xu, R., Greening, D.W., Zhu, H.J., Takahashi, N., & Simpson, R. J., 2016, Extracellular vesicle isolation and characterization: toward clinical

- application, *J Clin Invest*, 126(4):1152-62.
<https://doi.org/10.1172/JCI81129>.
- Yang, J.D., & Roberts, L.R., 2010, Hepatocellular carcinoma: A global view, *Nat Rev Gastroenterol Hepatol*, 7(8):448–458.
<https://doi.org/10.1038/nrgastro.2010.100>.
- Ye, Q., Ling, S., Zheng, S., & Xu, X., 2019, Liquid biopsy in hepatocellular carcinoma: circulating tumor cells and circulating tumor DNA, *Molecular Cancer*, 18(1):114. <https://doi.org/10.1186/s12943-019-1043-x>.
- Yin, M., Talwalkar, J.A., Glaser, K.J., Venkatesh, S.K., Chen, J., Manduca, A., & Ehman, R.L., 2011, Dynamic postprandial hepatic stiffness augmentation assessed with MR elastography in patients with chronic liver disease, *AJR Am J Roentgenol*, 197(1):64–70.
<https://doi.org/10.2214/AJR.10.5989>.
- Yoon, J.S., Kim, G., Lee, Y.R., et al., 2018, Clinical significance of microRNA-21 expression in disease progression of patients with hepatocellular carcinoma, *Biomark Med*, 12(10):1105-1114.
<https://doi.org/10.2217/bmm-2018-0096>.
- Yu, L., Ling, Y., & Wang, H., 2018, Role of nonresolving inflammation in hepatocellular carcinoma development and progression, *npj Precision Onc*, 2(6). <https://doi.org/10.1038/s41698-018-0048-z>.
- Yuen, M.F., Hou, J.L., & Chutaputti, A., 2009, Asia Pacific Working Party on Prevention of Hepatocellular Carcinoma: Hepatocellular carcinoma in the Asia pacific region, *J Gastroenterol Hepatol*, 24(3):346-353.
<https://doi.org/10.1111/j.1440-1746.2009.05784.x>.
- Zhang, J., Fujimoto, J., Zhang, J., et al., 2014, Intratumor heterogeneity in localized lung adenocarcinomas delineated by multiregion sequencing, *Science*, 346(6206):256-259.
<https://doi.org/10.1126/science.1256930>.
- Zhang, N., Hu, Z., Qiang, Y., & Zhu, X., 2019, Circulating miR-130b- and miR-21-based diagnostic markers and therapeutic targets for hepatocellular carcinoma, *Molecular genetics & genomic medicine*, 7(12):e1012.
<https://doi.org/10.1002/mgg3.1012>.
- Zhang, Z., Wang, J., Zeng, X., Li, D., Ding, M., Guan, R., Yuan, L., Zhou, Q., Guo, M., Xiong, M., Dong, L., Lu, W., 2017, Two-stage study of lung cancer risk modification by a functional variant in the 3'-untranslated region of *SMAD5* based on the bone morphogenetic protein pathway, *Mol Clin Oncol*. 8(1):38-46. <https://doi.org/10.3892/mco.2017.1490>.
- Zhu, K., Dai, Z., & Zhou, J., 2013, Biomarkers for hepatocellular carcinoma: progression in early diagnosis, prognosis, and personalized therapy, *Biomark Res*, 1(1):10. <https://doi.org/10.1186/2050-7771-1-10>.