Les modulations de l'environnement tumoral cancéreux par la propolis :

intérêt thérapeutique en oncologie intégrative



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BIBLIOGRAPHIE

- [1] Globocan Key Facts. Available from: https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf
- [2] Chan GC et al. 2013. The immunomodulatory and anticancer properties of propolis. Clin. Rev. Allergy Immunol., 44: 262-273.
- [2] de la Cruz-López KG et al. 2019. Lactate in the Regulation of Tumor Microenvironment and Therapeutic Approaches. Front. Oncol., 91143
- [4] Pérez-Tomás R & Pérez-Guillén I. 2020. Lactate in the Tumor Microenvironment: An Essential Molecule in Cancer Progression and Treatment. Cancers, 12: 3244.
- [5] Walenta S et al. 2000. High lactate levels predict likelihood of metastases, tumor recurrence, and restricted patient survival in human cervical cancers. Cancer Res., 60: 916-21.
- [6] Brizel DM et al. 2001. Elevated tumor lactate concentrations predict for an increased risk of metastases in head-and-neck cancer. Int J Radiat Oncol Biol Phys., 51: 349-53.
- [7] Walenta S et al. 1997. Correlation of high lactate levels in head and neck tumors with incidence of metastasis. Am J Pathol., 150: 409-15.
- [8] Hensley CT et al. 2016. Metabolic heterogeneity in human lung tumors. Cell, 164: 681-94.
- [9] Baek GH et al. 2014. MCT4 defines a glycolytic subtype of pancreatic cancer with poor prognosis and unique metabolic dependencies. Cell Rep., 9: 2233-49.
- [10] Bonuccelli G et al. 2010. Ketones and lactate "fuel" tumor growth and metastasis: evidence that epithelial cancer cells use oxidative mitochondrial metabolism. Cell Cycle, 9: 3506-14.
- [11] Gonzalez H et al. 2018. Roles of the immune system in cancer: from tumor initiation to metastatic progression. Genes Dev., 32: 1267-84.
- [12] Liu Y & Cao X. 2016. Immunosuppressive cells in tumor immune escape and metastasis. J Mol Med., 94: 509-22.
- [13] Dhup S et al. 2012. Multiple biological activities of lactic acid in cancer: influences on tumor growth, angiogenesis and metastasis. Curr Pharm Des., 18: 1319-30.
- [14] Pegram HJ et al. 2011. Activating and inhibitory receptors of natural killer cells. Immunol Cell Biol., 89: 216-24.
- [15] Lanier LL. 2009. Up on the tightrope: natural killer cell activation and inhibition. Nat Immunol., 9: 495-502.
- [16] Groh V et al. 2002. Tumour-derived soluble MIC ligands impair expression of NKG2D and T-cell activation. Nature., 419: 734-8.
- [17] Harmon C et al. 2019. Lactate-mediated acidification of tumor microenvironment induces apoptosis of liver-resident NK cells in colorectal liver metastasis. Cancer Immunol Res., 7: 335-46.
- [18] Bae EA et al. 2019. Roles of NKT cells in cancer immunotherapy. Arch Pharm Res., 42: 543-8.
- [19] Xie D et al. 2016. Lactic acid in tumor microenvironments causes dysfunction of NKT cells by interfering with mTOR signaling. Sci China Life Sci., 59: 1290-6.
- [20] Kumar A et al. 2019. Enhanced oxidative phosphorylation in NKT cells is essential for their survival and function. Proc Natl Acad Sci
- [21] Gupta S. 2014. Role of dendritic cells in innate and adaptive immune response in human aging. Exp Gerontol., 54: 47-52.
- [22] Steinman RM. 1991. The dendritic cell system and its role in immunogenicity. Annu Rev Immunol., 9: 271-96.
- [23] Kim B & Kim TH. 2018. Fundamental role of dendritic cells in inducing Th2 responses. Korean J Intern Med., 33: 483-9.
- [24] Deligeoroglou E et al. 2013. HPV infection: immunological aspects

- and their utility in future therapy. Infect Dis Obstet Gynecol., 2013: 540850.
- [25] Scott M et al. 2001. Cell-mediated immune response to human papillomavirus infection. J Allergy Clin Immunol., 8: 209-20.
 [26] Leone P et al. 2013. MHC class I antigen processing and presenting machinery: organization, function, and defects in tumor cells. J Natl
- [27] Andersen MH et al. 2006. Cytotoxic T cells. J Invest Dermatol., 126:

Cancer Inst., 105: 1172-87.

- [28] Nasi A et al. 2013. Dendritic cell reprogramming by endogenously produced lactic acid. J Immunol., 191: 3090-9.
- [29] Gu Yet al. 2008. Interleukin 10 suppresses Th17 cytokines secreted by macrophages and T cells. Eur J Immunol., 38: 1807-13.
- [30] Moore KW et al. 2001. Interleukin-10 and the Interleukin-10 Receptor. Annu Rev Immunol., 19: 683-765.
- [31] Zhao S et al. 2015. Serum IL-10 predicts worse outcome in cancer patients: a meta-analysis. PLoS ONE., 10: 1-15.
- [32] Shime H et al. 2008. Tumor-secreted lactic acid promotes IL-23/IL-17 proinflammatory pathway. J Immunol., 180: 7175-83.
- [33] Fischer K et al. 2007. Inhibitory effect of tumor cell-derived lactic acid on human T cells. Blood, 109: 3812-9.
- [34] Brand A et al. 2016. LDHA-associated lactic acid production blunts tumor immune-surveillance by T and NK cells. Cell Metab., 24: 657-
- [35] Daneshmandi S et al. 2019. Blockade of lactate dehydrogenase-A (LDH-A) improves efficacy of anti-programmed cell death-1 (PD-1) therapy in melanoma. Cancers, 11: 450.
- [36] San-Millán I et al. 2020. Is lactate an oncometabolite? evidence supporting a role for Lactate in the regulation of transcriptional activity of cancer-related genes in MCF7 breast cancer cells. Front. Oncol., 9:1536
- [37] Colegio OR et al. 2014. Functional polarization of tumour-associated macrophages by tumour- derived lactic acid. Nature, 513: 559-63.
- [38] Mu X et al. 2018. Tumor-derived lactate induces M2 macrophage polarization via the activation of the ERK/STAT3 signaling pathway in breast cancer. Cell Cycle, 17: 428-38.
- [39] Oršolic N et al. 2022. Molecular and Cellular Mechanisms of Propolis and Its Polyphenolic Compounds against Cancer. Int. J. Mol. Sci., 23: 10479.
- [40]Oršolic N & Bašic I. 2005. Antitumor, hematostimulative and radioprotective action of water-soluble derivative of propolis (WSDP). Biomed. Pharmacother., 59: 561-570.
- [41] Cardoso EO et al. 2017. Phenolic compounds alone or in combination may be involved in propolis effects on human monocytes. J. Pharm. Pharmacol., 69: 99-108.
- [42] Oršolic N et al. 2008. Benefits of use of propolis and related flavonoids against the toxicity of chemotherapeutic agents. In: Scientific Evidence of the Use of Propolis in Ethnomedicine, Oršolic N & Bašic I, Eds. Transworld Research Network: Trivandrum, India, pp. 195-222.
- [43] Bueno Silva B et al. 2017. Brazilian red propolis effects on peritoneal macrophage activity: Nitric oxide, cell viability, pro-inflammatory cytokines and gene expression. J. Ethnopharmacol., 207: 100-107.
- **[44]**Han S et al. 2002. Activation of murine macrophage cell line RAW264.7 by Korean propolis. Arch. Pharm. Res., 25: 895-902.
- [45] Oršolic N & Bašic I. 2007. Cancer chemoprevention by propolis and its polyphenolic compounds in experimental animals. In: Recent Progress in Medicinal Plants. Singh VK, Govil JN & Arunachalam C, Eds. Studium Press LLC: Houston, TX, USA, pp. 55-113.

- [46] Oršolic N & Bašic I. 2005. Antitumor, hematostimulative and radioprotective action of water-soluble derivative of propolis (WSDP). Biomed. Pharmacother., 59: 561-570.
- [47] Oršolic N et al. 2005. Effect of local administration of propolis and its polyphenolic compounds on the tumour formation and growth. Biol. Pharm. Bull., 28: 1928-1933.
- [48] Orsi RO et al. 2000. Immunomodulatory action of propolis on macrophage activation. J. Venom. Anim. Toxins, 6: 205-219.
- [49] Sforcin JM. 2007. Propolis and the immune system: A review. J. Ethnopharmacol., 113: 1-14.
- [50] Cardoso EO et al. 2017. Phenolic compounds alone or in combination may be involved in propolis effects on human monocytes. J. Pharm. Pharmacol., 69: 99-108.
- [51] Radovanovic V et al. 2019. Neurotoxic Effect of Ethanolic Extract of Propolis in the Presence of Copper Ions is Mediated through Enhanced Production of ROS and Stimulation of Caspase-3/7 Activity. Toxins, 11: 273.
- [52] Chang CI et al. 2001. Macrophage arginase promotes tumor cell growth and suppresses nitric oxide-mediated tumor cytotoxicity. Cancer Res., 61: 1100-1106.
- [53] Missima F et al. 2010. The effect of propolis on Th1/Th2 cytokine expression and production by melanoma-bearing mice submitted to stress. Phytother. Res., 24: 1501-1507.
- [54] Kimoto T et al. 1998. Apoptosis and suppression of tumor growth by artepillin C extracted from Brazilian propolis. Cancer Detect. Prev., 22: 506-515.
- [55] Ocaña MC et al. 2019. Metabolism within the tumor microenvironment and its implication on cancer progression: An ongoing therapeutic target. Med. Res. Rev., 39: 70-113.
- [56] De Santis MC et al. 2018. Signaling Pathways Regulating Redox Balance in Cancer Metabolism. Front. Oncol., 8: 126.
- [57] Goetzman ES & Prochownik EV. 2018. The Role fo rMyc in Coordinating Glycolysis, Oxidative Phosphorylation, Glutaminolysis, and Fatty Acid Metabolism in Normal and Neoplastic Tissues. Front. Endocrinol., 9: 129.
- [58] Gouirand V et al. 2018. Influence of the Tumor microenvironment on Cancer Cells Metabolic Reprogramming. Front. Oncol., 8: 117.
- [59] de la Cruz-López KG et al. 2019. Lactate in the Regulation of Tumor Microenvironment and Therapeutic Approaches. Front. Oncol., 9: 1143.
- **[60]** Cerella C et al. 2013. Natural compounds as regulators of the cancer cell metabolism. Int. J. Cell Biol., 2013: 639401.
- [61] Gao JL & Chen YG. 2015. Natural compounds regulate glycolysis in hypoxic tumor microenvironment. Biomed. Res. Int., 2015: 354143.
- [62] Shim CK et al. 2007. Inhibition effect of flavonoids on monocarboxylate transporter1 (MCTI) in Caco-2 cells. J. Pharm. Pharmacol., 59: 1515-1519
- [63] Jia L et al. 2018. Quercetin suppresses the mobility of breast cancer by suppressing glycolysis through Akt-mTOR pathway mediated autophagy induction. Life Sci., 208: 123-130.
- [64] Wang G et al. 2017. Strategies to Target Glucose Metabolism in Tumor Microenvironment on Cancer by Flavonoids. Nutr. Cancer, 69: 534-554.
- [65] Keating E & Martel F. 2018. Antimetabolic Effects of Polyphenols in Breast Cancer Cells: Focus on Glucose Uptake and Metabolism. Front. Nutr., 5: 25.
- [66] Colen CB et al. 2011. Metabolic targeting of lactate efflux by malignant glioma inhibits invasiveness and induces necrosis: An in vivo study. Neoplasia, 13: 620-632.
- [67] Pérez A et al. 2011. Hexose transporter GLUTI harbors several distinct regulatory binding sites for flavones and tyrphostins. Biochemistry, 50: 8834-8845.
- [68] Park JB. 1999. Flavonoids are potential inhibitors of glucose uptake in U937 cells. Biochem. Biophys. Res. Commun., 260: 568-574.
- [69] Kueck A et al. 2007. Resveratrol inhibits glucose metabolism in human ovarian cancer cells. Gynecol. Oncol., 107: 450-457.
- [70] Tan L et al. 2016. Resveratrol inhibits ovarian tumor growth in an in vivo mouse model. Cancer, 122, 722-729.
- [71] Jung KH et al. 2013. Resveratrol suppresses cancer cell glucose uptake by targeting reactive oxygen species-mediated hypoxiainducible factor-1α activation. J. Nucl. Med., 54: 2161-2167.
- [72] Salas M et al. 2013. Resolution of the direct interaction with and inhibition of the human GLUTI hexose transporter by resveratrol from its effect on glucose accumulation. Am. J. Physiol. Cell Physiol., 305: C90-C99.

- [73] Sohel M et al. 2022. Chemotherapeutic potential of hesperetin for cancer treatment, with mechanistic insights: A comprehensive review. Heliyon, 8: e08815.
- [74] Qian Y et al. 2014. Inhibitors of glucose transport and glycolysis as novel anticancer therapeutics. World J. Transl. Med., 3: 37-57.
- [75] Gonzalez-Menendez P et al. 2014. Regulation of GLUT transporters by flavonoids in androgen-sensitive and -insensitive prostate cancer cells. Endocrinology, 155: 3238-3250.
- [76] Tan L et al. 2016. Resveratrol inhibits ovarian tumor growth in an in vivo mouse model. Cancer. 122: 722-729.
- [77] Jung KH et al. 2013. Resveratrol suppresses cancer cell glucose uptake by targeting reactive oxygen species-mediated hypoxia-inducible factor-1α activation. J. Nucl. Med., 54: 2161-2167.
- [78] León D et al. 2017. Implications of Resveratrol on Glucose Uptake and Metabolism. Molecules, 22: 398.
- [79] Ishaq S & Nunn L. 2015. Helicobacter pylori and gastric cancer. A state of the art review. Gastroenterol. Hepatol. Bed Bench, 8 (Suppl. S1): S6-S14.
- [80] Farzaei MH et al. 2015. Role of dietary polyphenols in the management of peptic ulcer. World J. Gastroenterol., 21: 6499-64517.
- [81] Ruiz-Bustos P et al. 2023. Propolis: Antineoplastic Activity, Constituents, and Mechanisms of Action. Curr Top Med Chem., 23(18): 1753-1764.
- [82] Joyeux H & Ceballos L. 2024. Les 6 secrets des abeilles : En santé intégrative et familiale. Editions du Rocher.
- [83] Altabbal S et al. 2023. Propolis: A Detailed Insight of Its Anticancer Molecular Mechanisms. Pharmaceuticals (Basel), 16(3): 450.
- [84] Hermansyah D et al. 2022. The Potential Use of Propolis as an Adjunctive Therapy in Breast Cancers. Integrative Cancer Therapies, 21. doi: 10.1177/15347354221096868
- [85] Ebeid SA et al. 2016. Assessment of the radioprotective effect of propolis in breast cancer patients undergoing radiotherapy: new perspective for an old honey bee product. J. Radiat. Res. Appl. Sci., 9: 431-440.
- [86] Juanbeltz Zurbano R et al. 2017. Complementary medicine use in cancer patients receiving intravenous antineoplastic treatment. Farm Hosp., 41: 589-600.
- [87] Piredda M et al. 2017. Propolis in the prevention of oral mucositis in breast cancer patients receiving adjuvant chemotherapy: a pilot randomised controlled trial. Eur J Cancer Care., 26: e12757.
- [88] Darvishi N et al. 2020. Antioxidant and anti-inflammatory effects of oral propolis in patients with breast cancer treated with chemotherapy: a randomized controlled trial. J Herb Med., 23: 100385.
- [89] Davoodi SH et al. 2021. Oral propolis, nutritional status and quality of life with chemotherapy for breast cancer: a randomized, double-blind clinical trial. Nutr Cancer., 8: 1-9.