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FACULDADE DE MEDICINA

Carolina Mendonça Gorgulho

Efeito de Células Tumorais Estressadas e Seus Exosomos Sobre a Ativação de Células Dendríticas *in vitro*

Tese apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, para obtenção do título de Doutora em Patologia.

Orientador: Prof. Dr.Ramon Kaneno
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1. Cólon (Anatomia) - Câncer. 2. Imunoterapia. 3. Autofagia. 4. Quimioterapia. 5. Administração metronômica. 6. Resistência à drogas.

Palavras-chave: autofagia; câncer colorretal; imunoterapia; quimioresistência; quimioterapia metronômica.

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Chapter 1 – Review of the Literature

Developing immunotherapies for patients with colorectal cancer

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Abstract

Risk factors for colorectal cancer (CRC) include poor dietary habits, sedentarism and obesity, in addition to genetic syndromes that predispose individuals to this disease. Current treatment mainly relies on surgical excision and cytotoxic chemotherapies; immunotherapy with checkpoint inhibitors only plays a role in 4-6% of patients with MSI^{high} tumors. Tumor cells have means to limit apoptosis and utilize autophagy to survive chemotherapy leading to drug resistance and enhanced survival. Pharmacological or molecular inhibition of autophagy has been proposed to improve the efficacy of cytotoxic chemotherapy. In addition, immunotherapy with checkpoint inhibition has raised substantial interest, but most patients with CRC do not respond to this modality of treatment, despite the fact that colorectal tumors are frequently infiltrated with adaptive immune cells. Thus, the search for new therapies that can be combined with current approaches to increase their efficacy, and new knowledge of the biology of CRC are pivotal to improve the care of patients suffering from this disease. Here, we review the basic immunobiology of CRC, current 'state of the art' therapies and new therapeutic promises for the future.

Keywords: colorectal cancer, immunotherapy, autophagy, chemoresistance, metronomic chemotherapy, DAMPs, HMGB1, dendritic cells, T cells.

1.1 - Etiology and Epidemiology of Colorectal Cancer

Colorectal cancer (CRC) ranks among the third most frequent cancer in both sexes worldwide, excluding non-melanoma skin cancer, accounting for almost 10% of all diagnosed cancers (1). Although one of the most preventable and treatable types of cancers (2), recent years have seen a rising incidence of CRC, particularly in western countries, due to the ageing population, dietary habits, sedentarism and other largely modifiable lifestyle risk factors (1). The mortality rate has been decreasing since the 1980's, prior to the advent of modern screening studies (3). Calculation models to predict risk of colorectal cancer that include both genetic and environmental factors are better risk predictors than the models currently employed based solely on age and familial history (4).

About 75% of CRC patients develop sporadic disease while 15 to 20% have a positive familial history of CRC syndromes, including: 1) Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer (5)), characterized by mutations in mismatch repair (MMR) genes such as *MLH1*, *MSH2*, *MSH6* and *PMS2*, leading to microsatellite instability (MSI), and 2) familial adenomatous polyposis, which arises from acquired or hereditable (6) mutations in the APC gene, promoting development of colon cancer at a young age (1). An important molecular distinction between sporadic MSI and Lynch syndrome-associated CRC is that the latter does not present with *BRAF* mutations (5). Chronic colitis associated with inflammatory bowel disease is thought to be responsible for approximately 1% of CRC cases, but this number is decreasing, likely due to the success of anti-inflammatory therapies (7). Similar to other cancers, chronic inflammation is still a common anlage in patients with CRC (8).

CRC arises from accumulation of a succession of mutations that lead to genetic and epigenetic instability of normal epithelial cells, culminating in the formation of benign lesions known as aberrant crypts, which progress to adenomas and eventually to invasive cancer (1), in concert with local immune cells responding to the need for both barrier function and selective transport (9).

The identification of various polyp morphologies that can give rise to malignant tumors as well as the molecular pathways that lead to their formation and progression enables more

accurate stratification (10), hopefully leading to better treatment selection. To date, four individual common genomic/epigenomic profiles have been described in CRC: 1) chromosomal instability (the most common, characterized by the occurrence of aneuploidy) and responsive to checkpoint inhibitors; 2) MSI^{hi}, which displays a normal karyotype but unique mutations in DNA damage repair genes; 3) CpG island methylator phenotype, and 4) global DNA hypomethylation (6). These mutations converge on key signaling pathways that dictate the biological behavior of tumor cells. For example, one of the most well studied pathways that is altered in CRC is the Wnt – β-catenin pathway. Mutations in the *APC* gene prevent proteasomal degradation of the transcription factor β-catenin, leading to upregulated transcription and secretion of products of the *WNT* gene (6) and deregulated cell proliferation. Mutations in the transforming growth factor-β (TGF-β) gene (or of its receptors and other genes such as *SMAD4*) are associated with the formation and malignant transformation of benign lesions (11). Furthermore, *SMAD4* expression can be indicative of responsiveness to 5-fluorouracil (5-FU) (12). Activating mutations in the oncogene *KRAS* lead to constitutive activation of the mitogen activated kinase (MAPK) pathway via *BRAF* signaling, promoting cell proliferation and survival (6). The PI3K/AKT signaling pathway is also affected during colonic carcinogenesis, through mutations in *PIK3CA*. This promotes malignant transformation of adenomas and loss of expression of the tumor suppressor *PTEN*, found in up to 30% of CRC cases (6, 13).

CRC can be further divided into two subgroups, according to mutational burden: 1) heavily mutated tumors (>12 coding mutations per 10^6 DNA bases), which are MMR-deficient and present high MSI or 2) MMR-proficient tumors, with low MSI and therefore lower mutational burden (<8.24 mutations per 10^6 DNA bases) (10). This classification is especially important for the immunobiology of the disease and eligibility for immunotherapy, as discussed in detail below.

1.2 - Immunobiology of CRC

It is well accepted that the immune system, through both innate and adaptive mechanisms, is capable of recognizing and eliminating transformed cells, in a process termed immunosurveillance. Both T and B cells are essential for the establishment of an adaptive immune response. Maturation of these cells depend on the function of proteins rag 1 and 2,

involved in the recombination of *VDJ* genes of both T and B cell receptors (14, 15). *RAG*$^{-/-}$ immune deficient mice are more susceptible to the occurrence of both spontaneous and chemically induced tumors, providing experimental evidence for the immunosurveillance concept (16). Thus, we are naturally equipped with effector cells and molecules capable of mediating the elimination of tumors, measurable in both experimental models and human clinical settings, in the form of tumor-specific antibodies or appearance of infiltrating αβ and γδ T cells.

Killing of susceptible tumor cells mediates their 'culling' or selection, enabling emergence of cells resistant to immune effectors and retaining genes associated with survival, immune evasion, and ability to escape to so-called pre-metastatic niches (17, 18). Such niches have limited or absent tissue-resident memory cells (TRMs) responsible for immunosurveillance (19), thus facilitating immune evasion and migration to distant sites. These steps as amended are known as the three E's: elimination, equilibrium and escape (20), and now the two C's: culling (selection for more potent tumor cells) and 'calling' (emigration to distant sites).

Thus, almost all CRC patients present with immune infiltration of tumors, associated with the estimated 7-10 years of host-tumor interaction before clinical diagnosis is even ascertained. The presence of tumor infiltrating lymphocytes (TILs) is, in general, considered a marker of good prognosis and is associated with an improved overall survival (OS) (21-23). Infiltration of $CD8^+$ T cells within the tumor and at its margins is a better predictive factor of disease-free survival than the current applied TNM staging method (24), which uses size of the primary tumor (T), lymph node involvement (N) and presence of metastatic disease (M) as parameters. Additionally, patients who present with a Th1 gene signature have improved survival (25). CRC patients with large numbers of infiltrating NK cells also have longer survival rates (26). Similarly, the presence of NK cells in liver metastasis positively correlates with overall survival (OS) (27). The opposite seems to be the case for neutrophils, with infiltration being correlated with worse prognosis and more advanced stage of disease (28-30) although there is compelling evidence pointing to an anti-tumor supporting role for this population as well (31). Infiltration of myeloid-derived suppressor cells (MDSCs), associated with neutrophilic infiltration, in colorectal tumors is indicative of an unfavorable prognosis, being associated with nodal and distant metastasis and advanced stage of disease (32, 33). A meta-analysis of studies evaluating the association

between infiltration of tumor associated macrophages (TAMs) in several solid cancers and individual clinical parameters concluded that for CRC, TAMs are positively linked to improved OS, (although no distinction was made between M1 and M2 phenotypes) (34) and higher infiltration of $CD8^+$ T cells (35). The presence of TAMs in the invasive front of colon tumors correlates with a lower incidence of metastatic disease and improved OS (36). However, immature monocytes (which can give rise to TAMs and dendritic cells [DCs]) impair the activity of cytotoxic T lymphocyte (CTL) within tumors (37).

Although the main focus of conventional vaccination-based immunotherapies thus far has been on promoting antigen presentation in the lymph nodes, interaction between antigen presenting cells (APCs) and T cells also occurs within the tumor. A minor subset of DCs has been characterized within tumors as $BATF3^+$ $CD8\alpha^+$ $CD103^+$ DCs in mice and $CD141^+$ in humans, which are highly activated, possess alkaline endocytic compartments and are major producers of IL-12, therefore being very efficient at antigen cross-presentation as well as capable of promoting a TH1 response (38). They are transcriptionally driven by IRF8 and BATF3 and differentiate in the presence of the cytokines FLT3L and GM-CSF. These DCs are highly efficient, activating both naïve and previously activated tumor-specific CTLs *ex vivo*, albeit at higher numbers than normally found within tumors. Indeed, they are indispensable for *in vivo* tumor regression following adoptive cellular transfer, in models that exclude T cell priming in the lymph node. The transcriptional signature for this DCs subset in individual human cancers (including CRC) correlates with a favorable prognosis (38). $CD103^+$ DCs also appear to be important mediators of chemotherapy-induced tumor regression in mice, since depletion of myeloid cells (but not of $CD11b^+$ and $CD103^+$ DCs) ameliorates the anti-tumor effect of paclitaxel in an IL-12 dependent manner (39). Additionally, a transcriptional signature enriched for IL12A and IRF8 mRNA expression is predictive of complete responses to paclitaxel in human breast cancer (39). In the normal gut, DCs also generate T regulatory cells, in accordance with the highly tolerogenic environment of this tissue which is constantly exposed to food antigens, dead and dying cells, and the microbiota (40). $CD103^+$ DCs, however, apparently fail to do so in the colon of patients suffering from ulcerative colitis and induce production of pro-inflammatory cytokines by T cells co-cultured *ex vivo* with these DCs (41).

Even though the infiltration and persistence of certain immune populations can be a positive prognostic marker, it can also be detrimental in the context of chronic inflammation, which continuously generates oxidative stress, tissue and DNA damage, leading to transformation of normal epithelial cells and progression of existing tumors (42). Not only chronic inflammation but also the gut microbiome has been investigated regarding its role in carcinogenesis and tumor progression (42). Colonic tumors exhibit increased tissue permeability, facilitating penetration of commensal bacteria, activating myeloid immune cells within the tumor via MyD88 engagement, and thus perpetuating tumor-promoting inflammation (43). Commensal bacteria can also elicit inflammatory responses in an opportunistic manner via expression of virulence-associated genes. For example, CRC patients who are seropositive for *H. pylori* present with much higher levels of activated Th1 T cells than their seronegative counterparts when compared to healthy controls (44). *H. pylori* seropositive patients also display higher activity of the immunosuppressive enzyme IDO, suggesting that not only does *H. pylori* induce chronic inflammation in the CRC setting, but it can also mediate suppression of tumor-specific effector cells. *H. hepaticus* is another example of a microbe associated with the induction of colitis and CRC, in a variety of mouse models (45-47). *B. fragilis* infection promotes CRC in mice, with the participation of immuno-modulatory Th17 and γδ T cells (48, 49). Additionally, *B. fragilis* infection in CRC patients is correlated with a worse prognosis (42, 50-52). *In vitro* studies demonstrate that *E. faecalis* induces oxidative stress in immune cells, and DNA damage and genomic instability in colonic epithelial cells (53, 54).

Chronic inflammation also enhances gut susceptibility to tumor-promoting bacteria. Colibactin, a genotoxin produced by a strain of *E. coli*, induces hepatocyte growth factor (HGF) production, the major ligand for the Met membrane tyrosine kinase signaling receptor, thereby promoting tumor cell proliferation in a CRC xenograft model (55). Within the colon of patients with inflammatory bowel disease (IBD), colibactin-producing *E. coli* are enriched and associated with a worse prognosis (42, 56-58). In contrast, the balanced interplay between immunity and microbiota can either delay the onset of CRC or of its progression, suggesting that some components of our microbiome and their metabolites can serve a protective role, including the presence of *Bifidobacterium lactis* (59)*, Lactobacillus acidophilus* (60) and others.

3– References

1. Kuipers EJ, Grady WM, Lieberman D, Seufferlein T, Sung JJ, Boelens PG, et al. Colorectal cancer. Nat Rev Dis Primers. 2015;1:15065. Epub 2015/01/01. doi: 10.1038/nrdp.2015.65. PubMed PMID: 27189416; PubMed Central PMCID: PMCPMC4874655.
2. Force USPST, Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, Jr., et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;315(23):2564-75. Epub 2016/06/16. doi: 10.1001/jama.2016.5989. PubMed PMID: 27304597.
3. Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, et al. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer. 2010;116(3):544-73. Epub 2009/12/10. doi: 10.1002/cncr.24760. PubMed PMID: 19998273; PubMed Central PMCID: PMC3619726.
4. Jeon J, Du M, Schoen RE, Hoffmeister M, Newcomb PA, Berndt SI, et al. Determining Risk of Colorectal Cancer and Starting Age of Screening Based on Lifestyle, Environmental, and Genetic Factors. Gastroenterology. 2018;154(8):2152-64 e19. Epub 2018/02/20. doi: 10.1053/j.gastro.2018.02.021. PubMed PMID: 29458155; PubMed Central PMCID: PMCPMC5985207.
5. Domingo E, Laiho P, Ollikainen M, Pinto M, Wang L, French AJ, et al. BRAF screening as a low-cost effective strategy for simplifying HNPCC genetic testing. J Med Genet. 2004;41(9):664-8. Epub 2004/09/03. doi: 10.1136/jmg.2004.020651. PubMed PMID: 15342696; PubMed Central PMCID: PMCPMC1735885.
6. Grady WM, Pritchard CC. Molecular alterations and biomarkers in colorectal cancer. Toxicol Pathol. 2014;42(1):124-39. Epub 2013/11/02. doi: 10.1177/0192623313505155. PubMed PMID: 24178577; PubMed Central PMCID: PMCPMC3947043.
7. Jess T, Simonsen J, Jorgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. Gastroenterology. 2012;143(2):375-81 e1; quiz e13-4. Epub 2012/04/24. doi: 10.1053/j.gastro.2012.04.016. PubMed PMID: 22522090.
8. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140(6):883-99. Epub 2010/03/23. doi: 10.1016/j.cell.2010.01.025. PubMed PMID: 20303878; PubMed Central PMCID: PMCPMC2866629.
9. Sugi K, Musch MW, Field M, Chang EB. Inhibition of Na+,K+-ATPase by interferon gamma down-regulates intestinal epithelial transport and barrier function. Gastroenterology. 2001;120(6):1393-403. Epub 2001/04/21. doi: 10.1053/gast.2001.24045. PubMed PMID: 11313309.
10. Cancer Genome Atlas N. Comprehensive molecular characterization of human colon and rectal cancer. Nature. 2012;487(7407):330-7. Epub 2012/07/20. doi: 10.1038/nature11252. PubMed PMID: 22810696; PubMed Central PMCID: PMCPMC3401966.
11. Takaku K, Oshima M, Miyoshi H, Matsui M, Seldin MF, Taketo MM. Intestinal tumorigenesis in compound mutant mice of both Dpc4 (Smad4) and Apc genes. Cell. 1998;92(5):645-56. Epub 1998/03/20. doi: 10.1016/s0092-8674(00)81132-0. PubMed

PMID: 9506519.
12. Boulay JL, Mild G, Lowy A, Reuter J, Lagrange M, Terracciano L, et al. SMAD4 is a predictive marker for 5-fluorouracil-based chemotherapy in patients with colorectal cancer. Br J Cancer. 2002;87(6):630-4. Epub 2002/09/19. doi: 10.1038/sj.bjc.6600511. PubMed PMID: 12237773; PubMed Central PMCID: PMCPMC2364238.
13. Yu M, Trobridge P, Wang Y, Kanngurn S, Morris SM, Knoblaugh S, et al. Inactivation of TGF-beta signaling and loss of PTEN cooperate to induce colon cancer in vivo. Oncogene. 2014;33(12):1538-47. Epub 2013/04/23. doi: 10.1038/onc.2013.102. PubMed PMID: 23604118; PubMed Central PMCID: PMCPMC3883899.
14. Girschick HJ, Grammer AC, Nanki T, Mayo M, Lipsky PE. RAG1 and RAG2 expression by B cell subsets from human tonsil and peripheral blood. J Immunol. 2001;166(1):377-86. Epub 2000/12/21. doi: 10.4049/jimmunol.166.1.377. PubMed PMID: 11123315.
15. Mombaerts P, Iacomini J, Johnson RS, Herrup K, Tonegawa S, Papaioannou VE. RAG-1-deficient mice have no mature B and T lymphocytes. Cell. 1992;68(5):869-77. Epub 1992/03/06. doi: 10.1016/0092-8674(92)90030-g. PubMed PMID: 1547488.
16. Shankaran V, Ikeda H, Bruce AT, White JM, Swanson PE, Old LJ, et al. IFNgamma and lymphocytes prevent primary tumour development and shape tumour immunogenicity. Nature. 2001;410(6832):1107-11. Epub 2001/04/27. doi: 10.1038/35074122. PubMed PMID: 11323675.
17. Kaplan RN, Riba RD, Zacharoulis S, Bramley AH, Vincent L, Costa C, et al. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. Nature. 2005;438(7069):820-7. Epub 2005/12/13. doi: 10.1038/nature04186. PubMed PMID: 16341007; PubMed Central PMCID: PMC2945882.
18. Peinado H, Zhang H, Matei IR, Costa-Silva B, Hoshino A, Rodrigues G, et al. Pre-metastatic niches: organ-specific homes for metastases. Nat Rev Cancer. 2017;17(5):302-17. Epub 2017/03/18. doi: 10.1038/nrc.2017.6. PubMed PMID: 28303905.
19. de Vries NL, van Unen V, Ijsselsteijn ME, Abdelaal T, van der Breggen R, Farina Sarasqueta A, et al. High-dimensional cytometric analysis of colorectal cancer reveals novel mediators of antitumour immunity. Gut. 2019. Epub 2019/07/05. doi: 10.1136/gutjnl-2019-318672. PubMed PMID: 31270164.
20. Mittal D, Gubin MM, Schreiber RD, Smyth MJ. New insights into cancer immunoediting and its three component phases--elimination, equilibrium and escape. Current opinion in immunology. 2014;27:16-25. Epub 2014/02/18. doi: 10.1016/j.coi.2014.01.004. PubMed PMID: 24531241; PubMed Central PMCID: PMC4388310.
21. Huh JW, Lee JH, Kim HR. Prognostic significance of tumor-infiltrating lymphocytes for patients with colorectal cancer. Arch Surg. 2012;147(4):366-72. Epub 2012/04/18. doi: 10.1001/archsurg.2012.35. PubMed PMID: 22508783.
22. Nosho K, Baba Y, Tanaka N, Shima K, Hayashi M, Meyerhardt JA, et al. Tumour-infiltrating T-cell subsets, molecular changes in colorectal cancer, and prognosis: cohort study and literature review. J Pathol. 2010;222(4):350-66. Epub 2010/10/12. doi: 10.1002/path.2774. PubMed PMID: 20927778; PubMed Central PMCID: PMCPMC3033700.
23. Reissfelder C, Stamova S, Gossmann C, Braun M, Bonertz A, Walliczek U, et al. Tumor-specific cytotoxic T lymphocyte activity determines colorectal cancer patient prognosis. J Clin Invest. 2015;125(2):739-51. Epub 2015/01/07. doi: 10.1172/JCI74894.

PubMed PMID: 25562322; PubMed Central PMCID: PMCPMC4319435.
24. Mlecnik B, Tosolini M, Kirilovsky A, Berger A, Bindea G, Meatchi T, et al. Histopathologic-based prognostic factors of colorectal cancers are associated with the state of the local immune reaction. J Clin Oncol. 2011;29(6):610-8. Epub 2011/01/20. doi: 10.1200/JCO.2010.30.5425. PubMed PMID: 21245428.
25. Tosolini M, Kirilovsky A, Mlecnik B, Fredriksen T, Mauger S, Bindea G, et al. Clinical impact of different classes of infiltrating T cytotoxic and helper cells (Th1, th2, treg, th17) in patients with colorectal cancer. Cancer Res. 2011;71(4):1263-71. Epub 2011/02/10. doi: 10.1158/0008-5472.CAN-10-2907. PubMed PMID: 21303976.
26. Coca S, Perez-Piqueras J, Martinez D, Colmenarejo A, Saez MA, Vallejo C, et al. The prognostic significance of intratumoral natural killer cells in patients with colorectal carcinoma. Cancer. 1997;79(12):2320-8. Epub 1997/06/15. doi: 10.1002/(sici)1097-0142(19970615)79:12<2320::aid-cncr5>3.0.co;2-p. PubMed PMID: 9191519.
27. Donadon M, Hudspeth K, Cimino M, Di Tommaso L, Preti M, Tentorio P, et al. Increased Infiltration of Natural Killer and T Cells in Colorectal Liver Metastases Improves Patient Overall Survival. J Gastrointest Surg. 2017;21(8):1226-36. Epub 2017/05/26. doi: 10.1007/s11605-017-3446-6. PubMed PMID: 28536806.
28. Cetin B, Kaplan MA, Berk V, Ozturk SC, Benekli M, Isikdogan A, et al. Prognostic factors for overall survival in patients with metastatic colorectal carcinoma treated with vascular endothelial growth factor-targeting agents. Asian Pac J Cancer Prev. 2012;13(3):1059-63. Epub 2012/05/29. doi: 10.7314/apjcp.2012.13.3.1059. PubMed PMID: 22631638.
29. Paul B, O'Neil BH, McRee AJ. Checkpoint inhibition for colorectal cancer: progress and possibilities. Immunotherapy. 2016;8(6):693-704. Epub 2016/05/21. doi: 10.2217/imt-2016-0013. PubMed PMID: 27197538.
30. Rao HL, Chen JW, Li M, Xiao YB, Fu J, Zeng YX, et al. Increased intratumoral neutrophil in colorectal carcinomas correlates closely with malignant phenotype and predicts patients' adverse prognosis. PLoS One. 2012;7(1):e30806. Epub 2012/02/02. doi: 10.1371/journal.pone.0030806. PubMed PMID: 22295111; PubMed Central PMCID: PMCPMC3266280.
31. Oberg HH, Wesch D, Kalyan S, Kabelitz D. Regulatory Interactions Between Neutrophils, Tumor Cells and T Cells. Front Immunol. 2019;10:1690. Epub 2019/08/06. doi: 10.3389/fimmu.2019.01690. PubMed PMID: 31379875; PubMed Central PMCID: PMC6657370.
32. OuYang LY, Wu XJ, Ye SB, Zhang RX, Li ZL, Liao W, et al. Tumor-induced myeloid-derived suppressor cells promote tumor progression through oxidative metabolism in human colorectal cancer. J Transl Med. 2015;13:47. Epub 2015/02/02. doi: 10.1186/s12967-015-0410-7. PubMed PMID: 25638150; PubMed Central PMCID: PMCPMC4357065.
33. Sun HL, Zhou X, Xue YF, Wang K, Shen YF, Mao JJ, et al. Increased frequency and clinical significance of myeloid-derived suppressor cells in human colorectal carcinoma. World J Gastroenterol. 2012;18(25):3303-9. Epub 2012/07/12. doi: 10.3748/wjg.v18.i25.3303. PubMed PMID: 22783056; PubMed Central PMCID: PMCPMC3391769.
34. Zhang QW, Liu L, Gong CY, Shi HS, Zeng YH, Wang XZ, et al. Prognostic significance of tumor-associated macrophages in solid tumor: a meta-analysis of the literature. PLoS One. 2012;7(12):e50946. Epub 2013/01/04. doi: 10.1371/journal.pone.0050946. PubMed

PMID: 23284651; PubMed Central PMCID: PMCPMC3532403.
35. Zhao Y, Ge X, Xu X, Yu S, Wang J, Sun L. Prognostic value and clinicopathological roles of phenotypes of tumour-associated macrophages in colorectal cancer. Journal of cancer research and clinical oncology. 2019;145(12):3005-19. Epub 2019/10/28. doi: 10.1007/s00432-019-03041-8. PubMed PMID: 31650222.
36. Zhou Q, Peng RQ, Wu XJ, Xia Q, Hou JH, Ding Y, et al. The density of macrophages in the invasive front is inversely correlated to liver metastasis in colon cancer. J Transl Med. 2010;8:13. Epub 2010/02/10. doi: 10.1186/1479-5876-8-13. PubMed PMID: 20141634; PubMed Central PMCID: PMCPMC2841127.
37. Kusmartsev S, Nagaraj S, Gabrilovich DI. Tumor-associated CD8+ T cell tolerance induced by bone marrow-derived immature myeloid cells. J Immunol. 2005;175(7):4583-92. Epub 2005/09/24. doi: 10.4049/jimmunol.175.7.4583. PubMed PMID: 16177103; PubMed Central PMCID: PMCPMC1350970.
38. Broz ML, Binnewies M, Boldajipour B, Nelson AE, Pollack JL, Erle DJ, et al. Dissecting the Tumor Myeloid Compartment Reveals Rare Activating Antigen-Presenting Cells Critical for T Cell Immunity. Cancer Cell. 2014;26(6):938. Epub 2014/12/08. doi: 10.1016/j.ccell.2014.11.010. PubMed PMID: 28898680.
39. Ruffell B, Chang-Strachan D, Chan V, Rosenbusch A, Ho CM, Pryer N, et al. Macrophage IL-10 blocks CD8+ T cell-dependent responses to chemotherapy by suppressing IL-12 expression in intratumoral dendritic cells. Cancer Cell. 2014;26(5):623-37. Epub 2014/12/03. doi: 10.1016/j.ccell.2014.09.006. PubMed PMID: 25446896; PubMed Central PMCID: PMCPMC4254570.
40. Abraha AM, Ketema EB. Apoptotic pathways as a therapeutic target for colorectal cancer treatment. World journal of gastrointestinal oncology. 2016;8(8):583-91. Epub 2016/08/31. doi: 10.4251/wjgo.v8.i8.583. PubMed PMID: 27574550; PubMed Central PMCID: PMC4980648.
41. Matsuno H, Kayama H, Nishimura J, Sekido Y, Osawa H, Barman S, et al. CD103+ Dendritic Cell Function Is Altered in the Colons of Patients with Ulcerative Colitis. Inflamm Bowel Dis. 2017;23(9):1524-34. Epub 2017/07/13. doi: 10.1097/MIB.0000000000001204. PubMed PMID: 28700533.
42. Chen J, Pitmon E, Wang K. Microbiome, inflammation and colorectal cancer. Semin Immunol. 2017;32:43-53. Epub 2017/10/07. doi: 10.1016/j.smim.2017.09.006. PubMed PMID: 28982615.
43. Grivennikov SI, Wang K, Mucida D, Stewart CA, Schnabl B, Jauch D, et al. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. Nature. 2012;491(7423):254-8. Epub 2012/10/05. doi: 10.1038/nature11465. PubMed PMID: 23034650; PubMed Central PMCID: PMCPMC3601659.
44. Engin AB, Karahalil B, Karakaya AE, Engin A. Helicobacter pylori and serum kynurenine-tryptophan ratio in patients with colorectal cancer. World J Gastroenterol. 2015;21(12):3636-43. Epub 2015/04/04. doi: 10.3748/wjg.v21.i12.3636. PubMed PMID: 25834331; PubMed Central PMCID: PMCPMC4375588.
45. Fox JG, Ge Z, Whary MT, Erdman SE, Horwitz BH. Helicobacter hepaticus infection in mice: models for understanding lower bowel inflammation and cancer. Mucosal Immunol. 2011;4(1):22-30. Epub 2010/10/15. doi: 10.1038/mi.2010.61. PubMed PMID: 20944559; PubMed Central PMCID: PMCPMC3939708.
46. Kullberg MC, Jankovic D, Gorelick PL, Caspar P, Letterio JJ, Cheever AW, et al.

Bacteria-triggered CD4(+) T regulatory cells suppress Helicobacter hepaticus-induced colitis. J Exp Med. 2002;196(4):505-15. Epub 2002/08/21. doi: 10.1084/jem.20020556. PubMed PMID: 12186842; PubMed Central PMCID: PMCPMC2196050.

47. Mangerich A, Knutson CG, Parry NM, Muthupalani S, Ye W, Prestwich E, et al. Infection-induced colitis in mice causes dynamic and tissue-specific changes in stress response and DNA damage leading to colon cancer. Proc Natl Acad Sci U S A. 2012;109(27):E1820-9. Epub 2012/06/13. doi: 10.1073/pnas.1207829109. PubMed PMID: 22689960; PubMed Central PMCID: PMCPMC3390855.

48. Housseau F, Wu S, Wick EC, Fan H, Wu X, Llosa NJ, et al. Redundant Innate and Adaptive Sources of IL17 Production Drive Colon Tumorigenesis. Cancer Res. 2016;76(8):2115-24. Epub 2016/02/18. doi: 10.1158/0008-5472.CAN-15-0749. PubMed PMID: 26880802; PubMed Central PMCID: PMCPMC4873376.

49. Wu S, Rhee KJ, Albesiano E, Rabizadeh S, Wu X, Yen HR, et al. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat Med. 2009;15(9):1016-22. Epub 2009/08/25. doi: 10.1038/nm.2015. PubMed PMID: 19701202; PubMed Central PMCID: PMCPMC3034219.

50. Boleij A, Hechenbleikner EM, Goodwin AC, Badani R, Stein EM, Lazarev MG, et al. The Bacteroides fragilis toxin gene is prevalent in the colon mucosa of colorectal cancer patients. Clin Infect Dis. 2015;60(2):208-15. Epub 2014/10/12. doi: 10.1093/cid/ciu787. PubMed PMID: 25305284; PubMed Central PMCID: PMCPMC4351371.

51. Kasai C, Sugimoto K, Moritani I, Tanaka J, Oya Y, Inoue H, et al. Comparison of human gut microbiota in control subjects and patients with colorectal carcinoma in adenoma: Terminal restriction fragment length polymorphism and next-generation sequencing analyses. Oncol Rep. 2016;35(1):325-33. Epub 2015/11/10. doi: 10.3892/or.2015.4398. PubMed PMID: 26549775.

52. Viljoen KS, Dakshinamurthy A, Goldberg P, Blackburn JM. Quantitative profiling of colorectal cancer-associated bacteria reveals associations between fusobacterium spp., enterotoxigenic Bacteroides fragilis (ETBF) and clinicopathological features of colorectal cancer. PLoS One. 2015;10(3):e0119462. Epub 2015/03/10. doi: 10.1371/journal.pone.0119462. PubMed PMID: 25751261; PubMed Central PMCID: PMCPMC4353626.

53. Wang X, Allen TD, May RJ, Lightfoot S, Houchen CW, Huycke MM. Enterococcus faecalis induces aneuploidy and tetraploidy in colonic epithelial cells through a bystander effect. Cancer Res. 2008;68(23):9909-17. Epub 2008/12/03. doi: 10.1158/0008-5472.CAN-08-1551. PubMed PMID: 19047172; PubMed Central PMCID: PMCPMC2596646.

54. Wang X, Huycke MM. Extracellular superoxide production by Enterococcus faecalis promotes chromosomal instability in mammalian cells. Gastroenterology. 2007;132(2):551-61. Epub 2007/01/30. doi: 10.1053/j.gastro.2006.11.040. PubMed PMID: 17258726.

55. Cougnoux A, Dalmasso G, Martinez R, Buc E, Delmas J, Gibold L, et al. Bacterial genotoxin colibactin promotes colon tumour growth by inducing a senescence-associated secretory phenotype. Gut. 2014;63(12):1932-42. Epub 2014/03/25. doi: 10.1136/gutjnl-2013-305257. PubMed PMID: 24658599.

56. Arthur JC, Gharaibeh RZ, Muhlbauer M, Perez-Chanona E, Uronis JM, McCafferty J, et al. Microbial genomic analysis reveals the essential role of inflammation in bacteria-induced colorectal cancer. Nat Commun. 2014;5:4724. Epub 2014/09/04. doi:

10.1038/ncomms5724. PubMed PMID: 25182170; PubMed Central PMCID: PMCPMC4155410.
57. Bonnet M, Buc E, Sauvanet P, Darcha C, Dubois D, Pereira B, et al. Colonization of the human gut by E. coli and colorectal cancer risk. Clin Cancer Res. 2014;20(4):859-67. Epub 2013/12/18. doi: 10.1158/1078-0432.CCR-13-1343. PubMed PMID: 24334760.
58. Prorok-Hamon M, Friswell MK, Alswied A, Roberts CL, Song F, Flanagan PK, et al. Colonic mucosa-associated diffusely adherent afaC+ Escherichia coli expressing lpfA and pks are increased in inflammatory bowel disease and colon cancer. Gut. 2014;63(5):761-70. Epub 2013/07/13. doi: 10.1136/gutjnl-2013-304739. PubMed PMID: 23846483; PubMed Central PMCID: PMCPMC3995253.
59. Kim SW, Kim HM, Yang KM, Kim SA, Kim SK, An MJ, et al. Bifidobacterium lactis inhibits NF-kappaB in intestinal epithelial cells and prevents acute colitis and colitis-associated colon cancer in mice. Inflamm Bowel Dis. 2010;16(9):1514-25. Epub 2010/03/24. doi: 10.1002/ibd.21262. PubMed PMID: 20310012.
60. Mohamadzadeh M, Pfeiler EA, Brown JB, Zadeh M, Gramarossa M, Managlia E, et al. Regulation of induced colonic inflammation by Lactobacillus acidophilus deficient in lipoteichoic acid. Proc Natl Acad Sci U S A. 2011;108 Suppl 1:4623-30. Epub 2011/02/02. doi: 10.1073/pnas.1005066107. PubMed PMID: 21282652; PubMed Central PMCID: PMCPMC3063598.
61. Matzinger P. Tolerance, danger, and the extended family. Annual review of immunology. 1994;12:991-1045. Epub 1994/01/01. doi: 10.1146/annurev.iy.12.040194.005015. PubMed PMID: 8011301.
62. Janeway C. Immunogenicity signals 1,2,3 ... and 0. Immunology today. 1989;10(9):283-6. Epub 1989/09/01. PubMed PMID: 2590379.
63. Tang D, Kang R, Coyne CB, Zeh HJ, Lotze MT. PAMPs and DAMPs: signal 0s that spur autophagy and immunity. Immunological reviews. 2012;249(1):158-75. Epub 2012/08/15. doi: 10.1111/j.1600-065X.2012.01146.x. PubMed PMID: 22889221; PubMed Central PMCID: PMC3662247.
64. Enamorado M, Khouili SC, Iborra S, Sancho D. Genealogy, Dendritic Cell Priming, and Differentiation of Tissue-Resident Memory CD8(+) T Cells. Front Immunol. 2018;9:1751. Epub 2018/08/16. doi: 10.3389/fimmu.2018.01751. PubMed PMID: 30108585; PubMed Central PMCID: PMC6079237.
65. Hildner K, Edelson BT, Purtha WE, Diamond M, Matsushita H, Kohyama M, et al. Batf3 deficiency reveals a critical role for CD8alpha+ dendritic cells in cytotoxic T cell immunity. Science. 2008;322(5904):1097-100. Epub 2008/11/15. doi: 10.1126/science.1164206. PubMed PMID: 19008445; PubMed Central PMCID: PMC2756611.
66. Kazama H, Ricci JE, Herndon JM, Hoppe G, Green DR, Ferguson TA. Induction of immunological tolerance by apoptotic cells requires caspase-dependent oxidation of high-mobility group box-1 protein. Immunity. 2008;29(1):21-32. Epub 2008/07/18. doi: 10.1016/j.immuni.2008.05.013. PubMed PMID: 18631454; PubMed Central PMCID: PMC2704496.
67. Kang R, Chen R, Zhang Q, Hou W, Wu S, Cao L, et al. HMGB1 in health and disease. Mol Aspects Med. 2014;40:1-116. Epub 2014/07/11. doi: 10.1016/j.mam.2014.05.001. PubMed PMID: 25010388; PubMed Central PMCID: PMC4254084.
68. Pitt JM, Kroemer G, Zitvogel L. Immunogenic and Non-immunogenic Cell Death in the Tumor Microenvironment. Advances in experimental medicine and biology.

2017;1036:65-79. Epub 2017/12/25. doi: 10.1007/978-3-319-67577-0_5. PubMed PMID: 29275465.
69. Yatim N, Cullen S, Albert ML. Dying cells actively regulate adaptive immune responses. Nature reviews Immunology. 2017;17(4):262-75. Epub 2017/03/14. doi: 10.1038/nri.2017.9. PubMed PMID: 28287107.
70. Brusa D, Garetto S, Chiorino G, Scatolini M, Migliore E, Camussi G, et al. Post-apoptotic tumors are more palatable to dendritic cells and enhance their antigen cross-presentation activity. Vaccine. 2008;26(50):6422-32. Epub 2008/10/14. doi: 10.1016/j.vaccine.2008.08.063. PubMed PMID: 18848858.
71. Di Nicola M, Napoli S, Anichini A, Mortarini R, Romagnoli L, Magni M, et al. Dendritic cell viability is decreased after phagocytosis of apoptotic tumor cells induced by staurosporine or vaccinia virus infection. Haematologica. 2003;88(12):1396-404. Epub 2003/12/23. PubMed PMID: 14687994.
72. Kim HS, Choo YS, Koo T, Bang S, Oh TY, Wen J, et al. Enhancement of antitumor immunity of dendritic cells pulsed with heat-treated tumor lysate in murine pancreatic cancer. Immunology letters. 2006;103(2):142-8. Epub 2005/11/30. doi: 10.1016/j.imlet.2005.10.021. PubMed PMID: 16313973.
73. Feng H, Zeng Y, Graner MW, Katsanis E. Stressed apoptotic tumor cells stimulate dendritic cells and induce specific cytotoxic T cells. Blood. 2002;100(12):4108-15. Epub 2002/10/24. doi: 10.1182/blood-2002-05-1389. PubMed PMID: 12393401.
74. Shi H, Cao T, Connolly JE, Monnet L, Bennett L, Chapel S, et al. Hyperthermia enhances CTL cross-priming. J Immunol. 2006;176(4):2134-41. Epub 2006/02/04. doi: 10.4049/jimmunol.176.4.2134. PubMed PMID: 16455969.
75. Zappasodi R, Pupa SM, Ghedini GC, Bongarzone I, Magni M, Cabras AD, et al. Improved clinical outcome in indolent B-cell lymphoma patients vaccinated with autologous tumor cells experiencing immunogenic death. Cancer Res. 2010;70(22):9062-72. Epub 2010/10/05. doi: 10.1158/0008-5472.CAN-10-1825. PubMed PMID: 20884630.
76. Jie X, Hua L, Jiang W, Feng F, Feng G, Hua Z. Clinical application of a dendritic cell vaccine raised against heat-shocked glioblastoma. Cell biochemistry and biophysics. 2012;62(1):91-9. Epub 2011/09/13. doi: 10.1007/s12013-011-9265-6. PubMed PMID: 21909820.
77. Vulpis E, Soriani A, Cerboni C, Santoni A, Zingoni A. Cancer Exosomes as Conveyors of Stress-Induced Molecules: New Players in the Modulation of NK Cell Response. Int J Mol Sci. 2019;20(3). Epub 2019/02/03. doi: 10.3390/ijms20030611. PubMed PMID: 30708970; PubMed Central PMCID: PMC6387166.
78. Hedlund M, Nagaeva O, Kargl D, Baranov V, Mincheva-Nilsson L. Thermal- and oxidative stress causes enhanced release of NKG2D ligand-bearing immunosuppressive exosomes in leukemia/lymphoma T and B cells. PLoS One. 2011;6(2):e16899. Epub 2011/03/03. doi: 10.1371/journal.pone.0016899. PubMed PMID: 21364924; PubMed Central PMCID: PMC3045385.
79. Wang T, Gilkes DM, Takano N, Xiang L, Luo W, Bishop CJ, et al. Hypoxia-inducible factors and RAB22A mediate formation of microvesicles that stimulate breast cancer invasion and metastasis. Proc Natl Acad Sci U S A. 2014;111(31):E3234-42. Epub 2014/06/19. doi: 10.1073/pnas.1410041111. PubMed PMID: 24938788; PubMed Central PMCID: PMC4128139.
80. Bandari SK, Purushothaman A, Ramani VC, Brinkley GJ, Chandrashekar DS, Varambally S, et al. Chemotherapy induces secretion of exosomes loaded with

heparanase that degrades extracellular matrix and impacts tumor and host cell behavior. Matrix biology : journal of the International Society for Matrix Biology. 2018;65:104-18. Epub 2017/09/11. doi: 10.1016/j.matbio.2017.09.001. PubMed PMID: 28888912; PubMed Central PMCID: PMC5816689.

81. Vulpis E, Cecere F, Molfetta R, Soriani A, Fionda C, Peruzzi G, et al. Genotoxic stress modulates the release of exosomes from multiple myeloma cells capable of activating NK cell cytokine production: Role of HSP70/TLR2/NF-kB axis. Oncoimmunology. 2017;6(3):e1279372. Epub 2017/04/14. doi: 10.1080/2162402X.2017.1279372. PubMed PMID: 28405503; PubMed Central PMCID: PMC5384384.

82. Gobbo J, Marcion G, Cordonnier M, Dias AMM, Pernet N, Hammann A, et al. Restoring Anticancer Immune Response by Targeting Tumor-Derived Exosomes With a HSP70 Peptide Aptamer. J Natl Cancer Inst. 2016;108(3). Epub 2015/11/26. doi: 10.1093/jnci/djv330. PubMed PMID: 26598503.

83. Yang Y, Chen Y, Zhang F, Zhao Q, Zhong H. Increased anti-tumour activity by exosomes derived from doxorubicin-treated tumour cells via heat stress. International journal of hyperthermia : the official journal of European Society for Hyperthermic Oncology, North American Hyperthermia Group. 2015;31(5):498-506. Epub 2015/05/09. doi: 10.3109/02656736.2015.1036384. PubMed PMID: 25955015.

84. Gorgulho CM, Romagnoli GG, Bharthi R, Lotze MT. Johnny on the Spot-Chronic Inflammation Is Driven by HMGB1. Front Immunol. 2019;10:1561. Epub 2019/08/06. doi: 10.3389/fimmu.2019.01561. PubMed PMID: 31379812; PubMed Central PMCID: PMC6660267.

85. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017;67(3):177-93. Epub 2017/03/02. doi: 10.3322/caac.21395. PubMed PMID: 28248415.

86. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87-108. Epub 2015/02/06. doi: 10.3322/caac.21262. PubMed PMID: 25651787.

87. Bilen MA, Carlisle JW, Sonpavde G. The prospects for combination therapy with capecitabine in the rapidly evolving treatment landscape of renal cell carcinoma. Expert Opin Investig Drugs. 2018;27(2):163-70. Epub 2018/01/13. doi: 10.1080/13543784.2018.1427731. PubMed PMID: 29323560.

88. Wilson PM, Danenberg PV, Johnston PG, Lenz HJ, Ladner RD. Standing the test of time: targeting thymidylate biosynthesis in cancer therapy. Nat Rev Clin Oncol. 2014;11(5):282-98. Epub 2014/04/16. doi: 10.1038/nrclinonc.2014.51. PubMed PMID: 24732946.

89. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer. 2003;3(5):330-8. Epub 2003/05/02. doi: 10.1038/nrc1074. PubMed PMID: 12724731.

90. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol. 2010;28(31):4697-705. Epub 2010/10/06. doi: 10.1200/JCO.2009.27.4860. PubMed PMID: 20921465.

91. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a

randomized GERCOR study. J Clin Oncol. 2004;22(2):229-37. Epub 2003/12/06. doi: 10.1200/JCO.2004.05.113. PubMed PMID: 14657227.
92. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol. 2008;26(10):1626-34. Epub 2008/03/05. doi: 10.1200/JCO.2007.14.7116. PubMed PMID: 18316791.
93. Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med. 2013;369(11):1023-34. Epub 2013/09/13. doi: 10.1056/NEJMoa1305275. PubMed PMID: 24024839.
94. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335-42. Epub 2004/06/04. doi: 10.1056/NEJMoa032691. PubMed PMID: 15175435.
95. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007;25(12):1539-44. Epub 2007/04/20. doi: 10.1200/JCO.2006.09.6305. PubMed PMID: 17442997.
96. Mennonna D, Maccalli C, Romano MC, Garavaglia C, Capocefalo F, Bordoni R, et al. T cell neoepitope discovery in colorectal cancer by high throughput profiling of somatic mutations in expressed genes. Gut. 2017;66(3):454-63. Epub 2015/12/19. doi: 10.1136/gutjnl-2015-309453. PubMed PMID: 26681737; PubMed Central PMCID: PMC5534766.
97. Yarchoan M, Hopkins A, Jaffee EM. Tumor Mutational Burden and Response Rate to PD-1 Inhibition. N Engl J Med. 2017;377(25):2500-1. Epub 2017/12/21. doi: 10.1056/NEJMc1713444. PubMed PMID: 29262275; PubMed Central PMCID: PMCPMC6549688.
98. Ganesh K, Stadler ZK, Cercek A, Mendelsohn RB, Shia J, Segal NH, et al. Immunotherapy in colorectal cancer: rationale, challenges and potential. Nat Rev Gastroenterol Hepatol. 2019;16(6):361-75. Epub 2019/03/20. doi: 10.1038/s41575-019-0126-x. PubMed PMID: 30886395.
99. Franke AJ, Skelton WP, Starr JS, Parekh H, Lee JJ, Overman MJ, et al. Immunotherapy for Colorectal Cancer: A Review of Current and Novel Therapeutic Approaches. J Natl Cancer Inst. 2019. Epub 2019/07/20. doi: 10.1093/jnci/djz093. PubMed PMID: 31322663.
100. Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA Approval Summary: Pembrolizumab for the Treatment of Microsatellite Instability-High Solid Tumors. Clin Cancer Res. 2019;25(13):3753-8. Epub 2019/02/23. doi: 10.1158/1078-0432.CCR-18-4070. PubMed PMID: 30787022.
101. Mehrvarz Sarshekeh A, Overman MJ, Kopetz S. Nivolumab in the treatment of microsatellite instability high metastatic colorectal cancer. Future Oncol. 2018;14(18):1869-74. Epub 2018/02/24. doi: 10.2217/fon-2017-0696. PubMed PMID: 29473436; PubMed Central PMCID: PMC6088272.
102. Zhang H, Tang J, Li C, Kong J, Wang J, Wu Y, et al. MiR-22 regulates 5-FU sensitivity by inhibiting autophagy and promoting apoptosis in colorectal cancer cells. Cancer Lett. 2015;356(2 Pt B):781-90. Epub 2014/12/03. doi: 10.1016/j.canlet.2014.10.029. PubMed

PMID: 25449431.
103. Hynes NE, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. Nat Rev Cancer. 2005;5(5):341-54. Epub 2005/05/03. doi: 10.1038/nrc1609. PubMed PMID: 15864276.
104. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandala M, Cervantes A, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi64-72. Epub 2013/10/23. doi: 10.1093/annonc/mdt354. PubMed PMID: 24078664.
105. Copur S, Aiba K, Drake JC, Allegra CJ, Chu E. Thymidylate synthase gene amplification in human colon cancer cell lines resistant to 5-fluorouracil. Biochem Pharmacol. 1995;49(10):1419-26. Epub 1995/05/17. doi: 10.1016/0006-2952(95)00067-a. PubMed PMID: 7763285.
106. Nars MS, Kaneno R. Immunomodulatory effects of low dose chemotherapy and perspectives of its combination with immunotherapy. Int J Cancer. 2013;132(11):2471-8. Epub 2012/08/29. doi: 10.1002/ijc.27801. PubMed PMID: 22927096.
107. de la Cruz-Morcillo MA, Valero ML, Callejas-Valera JL, Arias-Gonzalez L, Melgar-Rojas P, Galan-Moya EM, et al. P38MAPK is a major determinant of the balance between apoptosis and autophagy triggered by 5-fluorouracil: implication in resistance. Oncogene. 2012;31(9):1073-85. Epub 2011/08/16. doi: 10.1038/onc.2011.321. PubMed PMID: 21841826.
108. Li J, Hou N, Faried A, Tsutsumi S, Takeuchi T, Kuwano H. Inhibition of autophagy by 3-MA enhances the effect of 5-FU-induced apoptosis in colon cancer cells. Ann Surg Oncol. 2009;16(3):761-71. Epub 2009/01/01. doi: 10.1245/s10434-008-0260-0. PubMed PMID: 19116755.
109. Sui X, Kong N, Wang X, Fang Y, Hu X, Xu Y, et al. JNK confers 5-fluorouracil resistance in p53-deficient and mutant p53-expressing colon cancer cells by inducing survival autophagy. Sci Rep. 2014;4:4694. Epub 2014/04/16. doi: 10.1038/srep04694. PubMed PMID: 24733045; PubMed Central PMCID: PMCPMC3986705.
110. Tang JC, Feng YL, Liang X, Cai XJ. Autophagy in 5-Fluorouracil Therapy in Gastrointestinal Cancer: Trends and Challenges. Chin Med J (Engl). 2016;129(4):456-63. Epub 2016/02/18. doi: 10.4103/0366-6999.176069. PubMed PMID: 26879020; PubMed Central PMCID: PMCPMC4800847.
111. Green DR, Galluzzi L, Kroemer G. Mitochondria and the autophagy-inflammation-cell death axis in organismal aging. Science. 2011;333(6046):1109-12. Epub 2011/08/27. doi: 10.1126/science.1201940. PubMed PMID: 21868666; PubMed Central PMCID: PMCPMC3405151.
112. Zheng HC. The molecular mechanisms of chemoresistance in cancers. Oncotarget. 2017;8(35):59950-64. Epub 2017/09/25. doi: 10.18632/oncotarget.19048. PubMed PMID: 28938696; PubMed Central PMCID: PMCPMC5601792.
113. Mizushima N. Autophagy: process and function. Genes Dev. 2007;21(22):2861-73. Epub 2007/11/17. doi: 10.1101/gad.1599207. PubMed PMID: 18006683.
114. Chude CI, Amaravadi RK. Targeting Autophagy in Cancer: Update on Clinical Trials and Novel Inhibitors. Int J Mol Sci. 2017;18(6). Epub 2017/06/18. doi: 10.3390/ijms18061279. PubMed PMID: 28621712; PubMed Central PMCID: PMCPMC5486101.
115. Buchser WJ, Laskow TC, Pavlik PJ, Lin HM, Lotze MT. Cell-mediated autophagy promotes cancer cell survival. Cancer Res. 2012;72(12):2970-9. Epub 2012/04/17. doi:

10.1158/0008-5472.CAN-11-3396. PubMed PMID: 22505650; PubMed Central PMCID: PMCPMC3505669.
116. Baginska J, Viry E, Berchem G, Poli A, Noman MZ, van Moer K, et al. Granzyme B degradation by autophagy decreases tumor cell susceptibility to natural killer-mediated lysis under hypoxia. Proc Natl Acad Sci U S A. 2013;110(43):17450-5. Epub 2013/10/09. doi: 10.1073/pnas.1304790110. PubMed PMID: 24101526; PubMed Central PMCID: PMCPMC3808626.
117. Cook KL, Warri A, Soto-Pantoja DR, Clarke PA, Cruz MI, Zwart A, et al. Hydroxychloroquine inhibits autophagy to potentiate antiestrogen responsiveness in ER+ breast cancer. Clin Cancer Res. 2014;20(12):3222-32. Epub 2014/06/15. doi: 10.1158/1078-0432.CCR-13-3227. PubMed PMID: 24928945; PubMed Central PMCID: PMCPMC4073207.
118. Finbloom DS, Silver K, Newsome DA, Gunkel R. Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. J Rheumatol. 1985;12(4):692-4. Epub 1985/08/01. PubMed PMID: 4057189.
119. Manic G, Obrist F, Kroemer G, Vitale I, Galluzzi L. Chloroquine and hydroxychloroquine for cancer therapy. Mol Cell Oncol. 2014;1(1):e29911. Epub 2014/01/01. doi: 10.4161/mco.29911. PubMed PMID: 27308318; PubMed Central PMCID: PMCPMC4905171.
120. Wang Y, Peng RQ, Li DD, Ding Y, Wu XQ, Zeng YX, et al. Chloroquine enhances the cytotoxicity of topotecan by inhibiting autophagy in lung cancer cells. Chin J Cancer. 2011;30(10):690-700. Epub 2011/10/01. doi: 10.5732/cjc.011.10056. PubMed PMID: 21959046; PubMed Central PMCID: PMCPMC4012269.
121. Haas NB, Appleman LJ, Stein M, Redlinger M, Wilks M, Xu X, et al. Autophagy Inhibition to Augment mTOR Inhibition: a Phase I/II Trial of Everolimus and Hydroxychloroquine in Patients with Previously Treated Renal Cell Carcinoma. Clin Cancer Res. 2019;25(7):2080-7. Epub 2019/01/13. doi: 10.1158/1078-0432.CCR-18-2204. PubMed PMID: 30635337.
122. Rangwala R, Leone R, Chang YC, Fecher LA, Schuchter LM, Kramer A, et al. Phase I trial of hydroxychloroquine with dose-intense temozolomide in patients with advanced solid tumors and melanoma. Autophagy. 2014;10(8):1369-79. Epub 2014/07/06. doi: 10.4161/auto.29118. PubMed PMID: 24991839; PubMed Central PMCID: PMC4203514.
123. Mahalingam D, Mita M, Sarantopoulos J, Wood L, Amaravadi RK, Davis LE, et al. Combined autophagy and HDAC inhibition: a phase I safety, tolerability, pharmacokinetic, and pharmacodynamic analysis of hydroxychloroquine in combination with the HDAC inhibitor vorinostat in patients with advanced solid tumors. Autophagy. 2014;10(8):1403-14. Epub 2014/07/06. doi: 10.4161/auto.29231. PubMed PMID: 24991835; PubMed Central PMCID: PMCPMC4203517.
124. Rangwala R, Chang YC, Hu J, Algazy KM, Evans TL, Fecher LA, et al. Combined MTOR and autophagy inhibition: phase I trial of hydroxychloroquine and temsirolimus in patients with advanced solid tumors and melanoma. Autophagy. 2014;10(8):1391-402. Epub 2014/07/06. doi: 10.4161/auto.29119. PubMed PMID: 24991838; PubMed Central PMCID: PMCPMC4203516.
125. Belounis A, Nyalendo C, Le Gall R, Imbriglio TV, Mahma M, Teira P, et al. Autophagy is associated with chemoresistance in neuroblastoma. BMC Cancer. 2016;16(1):891. Epub 2016/11/17. doi: 10.1186/s12885-016-2906-9. PubMed PMID: 27846885; PubMed Central PMCID: PMCPMC5109645.

126. Boone BA, Bahary N, Zureikat AH, Moser AJ, Normolle DP, Wu WC, et al. Safety and Biologic Response of Pre-operative Autophagy Inhibition in Combination with Gemcitabine in Patients with Pancreatic Adenocarcinoma. Ann Surg Oncol. 2015;22(13):4402-10. Epub 2015/04/24. doi: 10.1245/s10434-015-4566-4. PubMed PMID: 25905586; PubMed Central PMCID: PMCPMC4663459.
127. Liu LQ, Wang SB, Shao YF, Shi JN, Wang W, Chen WY, et al. Hydroxychloroquine potentiates the anti-cancer effect of bevacizumab on glioblastoma via the inhibition of autophagy. Biomed Pharmacother. 2019;118:109339. Epub 2019/09/24. doi: 10.1016/j.biopha.2019.109339. PubMed PMID: 31545270.
128. Malhotra J, Jabbour S, Orlick M, Riedlinger G, Guo Y, White E, et al. Phase Ib/II study of hydroxychloroquine in combination with chemotherapy in patients with metastatic non-small cell lung cancer (NSCLC). Cancer Treat Res Commun. 2019;21:100158. Epub 2019/09/15. doi: 10.1016/j.ctarc.2019.100158. PubMed PMID: 31521049.
129. Kinsey CG, Camolotto SA, Boespflug AM, Guillen KP, Foth M, Truong A, et al. Protective autophagy elicited by RAF-->MEK-->ERK inhibition suggests a treatment strategy for RAS-driven cancers. Nat Med. 2019;25(4):620-7. Epub 2019/03/06. doi: 10.1038/s41591-019-0367-9. PubMed PMID: 30833748; PubMed Central PMCID: PMCPMC6452642.
130. Bryant KL, Stalnecker CA, Zeitouni D, Klomp JE, Peng S, Tikunov AP, et al. Combination of ERK and autophagy inhibition as a treatment approach for pancreatic cancer. Nat Med. 2019;25(4):628-40. Epub 2019/03/06. doi: 10.1038/s41591-019-0368-8. PubMed PMID: 30833752; PubMed Central PMCID: PMCPMC6484853.
131. Woo IS, Jung YH. Metronomic chemotherapy in metastatic colorectal cancer. Cancer Lett. 2017;400:319-24. Epub 2017/03/10. doi: 10.1016/j.canlet.2017.02.034. PubMed PMID: 28274890.
132. Kaneno R, Shurin GV, Kaneno FM, Naiditch H, Luo J, Shurin MR. Chemotherapeutic agents in low noncytotoxic concentrations increase immunogenicity of human colon cancer cells. Cell Oncol (Dordr). 2011;34(2):97-106. Epub 2011/02/04. doi: 10.1007/s13402-010-0005-5. PubMed PMID: 21290210.
133. Lennernas B, Albertsson P, Damber JE, Norrby K. Antiangiogenic effect of metronomic paclitaxel treatment in prostate cancer and non-tumor tissue in the same animals: a quantitative study. APMIS. 2004;112(3):201-9. Epub 2004/05/22. doi: 10.1111/j.1600-0463.2004.apm1120306.x. PubMed PMID: 15153162.
134. Singletary SE. Multidisciplinary frontiers in breast cancer management: a surgeon's perspective. Cancer. 2007;109(6):1019-29. Epub 2007/02/14. doi: 10.1002/cncr.22519. PubMed PMID: 17295294.
135. De Almeida CV, Zamame JA, Romagnoli GG, Rodrigues CP, Magalhaes MB, Amedei A, et al. Treatment of colon cancer cells with 5-fluorouracil can improve the effectiveness of RNA-transfected antitumor dendritic cell vaccine. Oncol Rep. 2017;38(1):561-8. Epub 2017/06/07. doi: 10.3892/or.2017.5692. PubMed PMID: 28586072.
136. Tsai CC, Qiu JT, Tseng CW, Hsu YC. Low-dose metronomic chemotherapy with cisplatin enhanced immunity in a murine model of ectopic cervical cancer. Clin Exp Pharmacol Physiol. 2016;43(2):251-8. Epub 2015/11/07. doi: 10.1111/1440-1681.12515. PubMed PMID: 26541904.
137. Kaneno R, Shurin GV, Tourkova IL, Shurin MR. Chemomodulation of human dendritic cell function by antineoplastic agents in low noncytotoxic concentrations. J

Transl Med. 2009;7:58. Epub 2009/07/14. doi: 10.1186/1479-5876-7-58. PubMed PMID: 19591684; PubMed Central PMCID: PMCPMC2716306.
138. Livesey KM, Kang R, Vernon P, Buchser W, Loughran P, Watkins SC, et al. p53/HMGB1 complexes regulate autophagy and apoptosis. Cancer Res. 2012;72(8):1996-2005. Epub 2012/02/22. doi: 10.1158/0008-5472.CAN-11-2291. PubMed PMID: 22345153; PubMed Central PMCID: PMC3417120.
139. Maiuri MC, Zalckvar E, Kimchi A, Kroemer G. Self-eating and self-killing: crosstalk between autophagy and apoptosis. Nature reviews Molecular cell biology. 2007;8(9):741-52. Epub 2007/08/25. doi: 10.1038/nrm2239. PubMed PMID: 17717517.
140. Shimizu S, Kanaseki T, Mizushima N, Mizuta T, Arakawa-Kobayashi S, Thompson CB, et al. Role of Bcl-2 family proteins in a non-apoptotic programmed cell death dependent on autophagy genes. Nature cell biology. 2004;6(12):1221-8. Epub 2004/11/24. doi: 10.1038/ncb1192. PubMed PMID: 15558033.
141. Yu J, Zhang L. PUMA, a potent killer with or without p53. Oncogene. 2008;27 Suppl 1:S71-83. Epub 2009/07/31. doi: 10.1038/onc.2009.45. PubMed PMID: 19641508; PubMed Central PMCID: PMC2860432.
142. Tasdemir E, Maiuri MC, Galluzzi L, Vitale I, Djavaheri-Mergny M, D'Amelio M, et al. Regulation of autophagy by cytoplasmic p53. Nature cell biology. 2008;10(6):676-87. Epub 2008/05/06. doi: 10.1038/ncb1730. PubMed PMID: 18454141; PubMed Central PMCID: PMC2676564.
143. Ludwig N, Razzo BM, Yerneni SS, Whiteside TL. Optimization of cell culture conditions for exosome isolation using mini-size exclusion chromatography (mini-SEC). Experimental cell research. 2019;378(2):149-57. Epub 2019/03/13. doi: 10.1016/j.yexcr.2019.03.014. PubMed PMID: 30857972.
144. Dougherty GJ, Murdoch S, Hogg N. The function of human intercellular adhesion molecule-1 (ICAM-1) in the generation of an immune response. European journal of immunology. 1988;18(1):35-9. Epub 1988/01/01. doi: 10.1002/eji.1830180107. PubMed PMID: 3257922.
145. Jeong JU, Uong TNT, Chung WK, Nam TK, Ahn SJ, Song JY, et al. Effect of irradiation-induced intercellular adhesion molecule-1 expression on natural killer cell-mediated cytotoxicity toward human cancer cells. Cytotherapy. 2018;20(5):715-27. Epub 2018/03/25. doi: 10.1016/j.jcyt.2018.01.010. PubMed PMID: 29572116.
146. Archimbaud E, Thomas X, Campos L, Magaud JP, Dore JF, Fiere D. Expression of surface adhesion molecules CD54 (ICAM-1) and CD58 (LFA-3) in adult acute leukemia: relationship with initial characteristics and prognosis. Leukemia. 1992;6(4):265-71. Epub 1992/04/01. PubMed PMID: 1375302.
147. Van Der Kraak L, Goel G, Ramanan K, Kaltenmeier C, Zhang L, Normolle DP, et al. 5-Fluorouracil upregulates cell surface B7-H1 (PD-L1) expression in gastrointestinal cancers. J Immunother Cancer. 2016;4:65. Epub 2016/10/26. doi: 10.1186/s40425-016-0163-8. PubMed PMID: 27777774; PubMed Central PMCID: PMC5067917.
148. Lehmann BD, Paine MS, Brooks AM, McCubrey JA, Renegar RH, Wang R, et al. Senescence-associated exosome release from human prostate cancer cells. Cancer Res. 2008;68(19):7864-71. Epub 2008/10/03. doi: 10.1158/0008-5472.CAN-07-6538. PubMed PMID: 18829542; PubMed Central PMCID: PMC3845029.
149. Yu X, Harris SL, Levine AJ. The regulation of exosome secretion: a novel function of the p53 protein. Cancer Res. 2006;66(9):4795-801. Epub 2006/05/03. doi: 10.1158/0008-5472.CAN-05-4579. PubMed PMID: 16651434.

150. Beninson LA, Brown PN, Loughridge AB, Saludes JP, Maslanik T, Hills AK, et al. Acute stressor exposure modifies plasma exosome-associated heat shock protein 72 (Hsp72) and microRNA (miR-142-5p and miR-203). PLoS One. 2014;9(9):e108748. Epub 2014/09/27. doi: 10.1371/journal.pone.0108748. PubMed PMID: 25259839; PubMed Central PMCID: PMC4178201.
151. Fleshner M, Crane CR. Exosomes, DAMPs and miRNA: Features of Stress Physiology and Immune Homeostasis. Trends in immunology. 2017;38(10):768-76. Epub 2017/08/26. doi: 10.1016/j.it.2017.08.002. PubMed PMID: 28838855; PubMed Central PMCID: PMC5624844.
152. Patente TA, Pinho MP, Oliveira AA, Evangelista GCM, Bergami-Santos PC, Barbuto JAM. Human Dendritic Cells: Their Heterogeneity and Clinical Application Potential in Cancer Immunotherapy. Front Immunol. 2018;9:3176. Epub 2019/02/06. doi: 10.3389/fimmu.2018.03176. PubMed PMID: 30719026; PubMed Central PMCID: PMC6348254.