

CYTOSTATIC CANCER THERAPY MODULATES MONOCYTE-MACROPHAGE CELL FUNCTIONS: HOW IT IMPACTS ON TREATMENT OUTCOMES

M. Patysheva^{1,2,}, M. Stakheyeva^{1,2}, I. Larionova^{1,2}, A. Fedorov², J. Kzhyshkowska^{1,3}, N. Cherdyntseva^{1,2}*

¹Tomsk State University, Tomsk 634050, Russia

*²Cancer Research Institute, Tomsk National Research Medical Center of Russian Academy of Sciences,
Tomsk 634009, Russia*

*³Institute of Transfusion Medicine and Immunology, Medical Faculty Mannheim,
University of Heidelberg, Theodor-Kutzer-Ufer, 1-3, Mannheim 68167, Germany*

Macrophages are important effectors of innate immunity and the key component of the tumor microenvironment strongly influencing cancer disease outcome and efficiency of cancer therapy. Moreover, recent data have shown that monocytes as macrophage precursors can impact on tumor ability to progression. It's well known that although tumor-associated macrophages consist of diverse populations, in general, they have tumor-supporting activity. To change tumor-supporting state of tumor-associated macrophages toward tumor-inhibiting mode is one of prospective aims of modern cancer immunotherapy. Cytostatics seems to be possible tools to achieve this aim, because recently it has been shown that chemo- and radiotherapy possess immunomodulatory effects. Most of the findings are related to lymphocytes — T-lymphocytes and NK-cells, but not to monocyte/macrophage lineage. In the review, we have analyzed how cytostatic drugs influence the properties of monocyte/macrophage lineage cells to prospect using of chemotherapy to enhance their antitumor activity.

Key Words: tumor-associated macrophages, monocytes, cytostatic therapy, immunomodulation, tumor progression.

Despite the fact that many new approaches to cancer treatment are now available, cytostatic chemotherapy still remains the mainstream in the management of cancer patients. The therapeutic effect of a cytostatic drug is provided by antiproliferative action leading to cytorreduction of tumor cells [1]. Since cytostatic agents affect cells that are actively growing and dividing, they are characterized by low selectivity and serious adverse effects on organs and tissues of the body.

The immune system, which has a high proliferative potential, is also adversely affected by cytostatics. Leukopenia and immunosuppression are frequent causes of anticancer treatment discontinuation. On the other hand, there are many reports highlighting immunomodulatory effects of cytotoxic drugs [2–4]. Under certain conditions, radiation and drug therapy switch off the phenomenon of tumor escape from immune surveillance and restore tumor-induced immune response, thereby leading to an increase in the therapeutic effectiveness. Antitumor immune response can be primed by immunogenic cell death caused by some cytostatic agents [2].

Immunomodulatory effects of chemotherapy are well described for lymphocytes [5], which are special cytotoxic effectors of the immune response, but they are little studied for monocyte/macrophage lineage cells. However it's well known that monocytes/macrophages play a key role in the pathological processes associated with chronic inflammation, such as cardiovascular and autoimmune diseases, transplant responses, and, particularly, cancer [6]. Due to functional plasticity, macrophages can vary their properties, showing both cytotoxic pro-inflammatory (M1), and growth-stimulatory anti-inflammatory (M2) type of polarization [7]. Nowadays, macrophage reprogramming from M2 to M1 polarization is one of the general challenges in cancer immunotherapy [8–11].

Basing on revealed immunomodulatory effects of cytostatics, a possibility to change macrophage functional state toward antitumor one with the use of some chemotherapeutic agents or regimens would be expected. But, unlike lymphocytes, cells of monocyte/macrophage lineage have low proliferation activity, and, accordingly, they are not susceptible to cytotoxic effects of chemotherapeutic agents [12]. Likely, some effects of cytostatics, differed from cytotoxic depletion, should modulate a functional state of monocyte/macrophage lineage cells. In the review, we have analyzed how cytostatic drugs influence properties of monocyte/macrophage lineage cells to prospect using of chemotherapy to enhance their antitumor activity.

MONOCYTES AND TUMOR-ASSOCIATED MACROPHAGES ARE INTERCONNECTED DURING CANCER PROGRESSION

It is well known that most of tissue macrophages derive from embryonic progenitors of the yolk sac and

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*Correspondence: E-mail: marinapatysh@gmail.com

Abbreviations used: 5-FU – 5-fluorouracil; BET – bromodomain and extra-terminal motif proteins; CSF1 – colony stimulating factor; DC – dendritic cell; DNMT – DNA methyltransferase; EMT – epithelial-mesenchymal transition; HDAC – histone deacetylase; HDM – histone demethylase; HMT – histone methyltransferase; M-CSF – macrophage colony stimulating factor; MCP-1 (CCL2) – monocyte chemoattractant protein 1; MHC II – major histocompatibility complex class II; MMP – matrix metalloprotease; NK – natural killer; TAM – tumor-associated macrophages; TET – ten-eleven translocation proteins; TIE2 – tyrosine-protein kinase receptor; TLR – Toll-like receptor; TNF- α – tumor necrosis factor alpha; VEGF – vascular endothelial growth factor.

fetal liver [13, 14]; however, in pathological conditions, including cancer, monocytes remain the main source of macrophages and dendritic cells (DC) in tissues. Although it was originally believed that a common hematopoietic stem cell was a precursor to monocytes, granulocytes and DC [15], recent data obtained by the massively parallel single-cell RNA-seq of hematopoietic cells indicated the existence of precommitted stem cell populations in the bone marrow for the formation of each separate subpopulation of monocytes [16].

Circulating monocytes have proven to contribute to the vast majority of tumor-associated macrophages (TAMs) infiltrated in mouse breast and lung tumors [17, 18]; and TAMs can be continuously and quickly replaced during cancer progression [17–19]. TAMs can proliferate in some tumors, although TAMs amplification is mainly due to the recruitment of circulating precursors [17–19]. The migration of monocytes from the bone marrow or spleen into the bloodstream and then into the tumor tissue occurs via CCR2-CCL2 axis. At the same time, CCL2 (monocyte chemoattractant protein 1 (MCP-1)) themselves attract resources for the formation of TAMs [20].

In addition, Franklin *et al.* [21] have shown that TAMs proliferate upon their differentiation from inflammatory monocytes, expressing the vascular cell adhesion protein (VCAM) adhesion molecule. Unlike TAMs, subcapsular sinus macrophages that are not derived from circulating monocytes are able to suppress the progression of melanoma in mice by limiting the systemic spread of tumor cells in the tumor-draining lymph nodes [22]. This fact confirms the hypothesis that the tumor modulates newly arrived TAMs to promote tumor progression.

It has been established that various phenotypes of monocytes and macrophages during the development and progression of cancer are regulated by epigenetic modifications. Programs for the differentiation and activation of monocytes to be matured into macrophages are realized via a significant epigenetic remodeling, such as histone modifications (acetylation and methylation), DNA methylation, miRNAs and long non-coding RNAs. Enzymes that control the epigenetic profile, such as DNA methyltransferase (DNMT) [23, 24], ten-eleven translocation proteins (TET) [25], histone methyltransferase (HMT) [26–32], histone demethylase (HDM) [33–36], histone deacetylase (HDAC) [37–41], bromodomain and extra-terminal motif proteins (BET) [42] have been shown to participate in the epigenetic regulation of M1 and M2 macrophage polarization (Table). More recently, Letai *et al.* (Dana Farber Cancer Institute, Boston, Massachusetts, USA) have demonstrated that TMP195, a class IIa histone deacetylase inhibitor (HDACs), promotes the involvement of inflammatory macrophages in murine breast carcinomas, leading to the initiation of a therapeutically relevant immune response [43]. Moreover, treatment with TMP195 results in more marked transcriptional changes in monocytes compared to lymphocytes [44]. Guerriero *et al.* [43] have

shown that the control of the function of enzymes that regulate the epigenetic profile of macrophages can result in M1 antitumor phenotype formation. These results promise new strategies for unlocking the antitumor potential of TAMs based on selective epigenetic modifications [45, 46].

Table. Epigenetic enzymes involved in macrophage polarization to M1 or M2

Epigenetic enzymes family	M1	M2	Reference
DNMT	DNMT1, DNMT3b	DNMT3b	[23], [24]
TET	TET2		[25]
HMT	PRMT1, ASH1, EZH1, EZH2, EHMT2(G9A), MLL1, MLL4, SET7, SETDB1, SETDB2, SMYD2, SMYD5, SUV39H2, SUV40H1, SUV40H2	PRMT1	[26–32]
HDM	AOI1,2, JMJD2, JMJD3, UTX	JMJD3	[33–36]
HDAC	HDAC1-7, HDAC11, SIRT1, SIRT2, SIRT6	HDAC3, HDAC4, SIRT2	[37–41]
BET	BET		[42]

Note: PRMT1 – protein methyltransferases 1; ASH1 – absent, small, or homeotic disc 1; EZH1,2 – enhancer of zeste homolog 1,2; EHMT2 (G9A) – histone-lysine N-methyltransferase-2 (G9A); MLL1,4 – mixed-lineage leukemia protein 1,4; SET7 – SET domain-containing protein 7; SETDB1,2 – SET domain-containing protein 2; SMYD2,5 – SET and MYND domain-containing protein 5; SUV39H2 – suppressor of variegation 3-9 homolog 2; SUV40H1,2 – suppressor of variegation 4-0 homolog 2; AOI1,2 – amine oxidase, flavin-containing 1,2; JMJD2,3 – jumonji domain-containing 2,3; UTX – ubiquitously transcribed tetratricopeptide repeat protein X; SIRT1,2,6 – sirtuin 1,2,6.

The tumor microenvironment is known to play an important role in tumor growth and response to cancer therapy, dramatically contributing to endowing cancer disease outcome. Due to biological plasticity, different subpopulations of macrophages can exhibit a range of opposite functions even within the same tumor that are provided by the heterogeneity of interaction between tumor and microenvironment [47]. Pro- or antitumor activity of each TAM subpopulation is determined by the microenvironment conditions in different tumor sites [48–50]. Conventionally, all TAMs are considered to be divided into two subpopulations: M1 – anti-tumor, with pro-inflammatory activity or tumor promoting M2-like, with anti-inflammatory activity [51, 52]. In addition, Sainz *et al.* [47] have found separate functional subpopulations of TAMs – supporting angiogenesis, stimulating metastasis, activating the epithelial-mesenchymal transition (EMT), or suppressing the immune response. However, it was reported TAMs function can be significantly altered during the chemotherapy resulting in activation of the antitumor immune response [2].

CYTOSTATIC TREATMENT MODULATES THE FUNCTION OF MONOCYTES AND MACROPHAGES

Chemotherapy agents can modulate tumor promoting- or inhibiting-tumor activity of monocytes/macrophages at each sequential stages of a linear development process, including proliferation of monocytes from progenitor cells in the bone marrow; recruitment and migration to the tissue, particularly, the tumor; functional maturation/polarization; differentiation and biological functioning [53].

Cytostatic agents impact on the proliferation of monocytes. Chemotherapy is known to deplete hematopoietic monocytic germ leading to monocytopenia [54, 55]. The decrease in the total number of monocytes is not directly associated with the development of immunodeficiency disorders, which are typically caused by the reduction in the total number of lymphocytes and neutrophils. However, a correlation between the number of circulating monocytes and the number of neutrophils is observed [56]. Apparently, this is mediated by a similarity in origin but difference in biology and function between these cells populations. Thus, the response of monocyte/macrophage cells to cytostatic treatment are most likely realized due to a change in the function of these cells.

Chemotherapy activates monocyte recruitment and migration. Cytostatic agents have a pronounced effect on the recruitment of monocytes from the bone marrow and migration to the tumor. Cyclophosphamide was shown to stimulate the recruitment of DC, macrophages and natural killer (NK) cells into the tumor [57, 58]. Nakasone *et al.* [58] revealed monocyte recruitment increasing in MMTV-PyMT (mouse model of breast cancer metastasis) treated with doxorubicin. The increased TAM infiltration after chemotherapy was also demonstrated in patients with breast cancer [58, 59] and glioblastoma [60].

The destruction of tumor cells by cytostatic agents induces production of specific tumor derived factors aimed at restoring their viability on the condition of wound healing where monocytes play important role in tissue repair [61]. In the case of tumor monocytes are required to be attracted to tumor site under the influence of tumor derivatives such as macrophage colony stimulating factor (M-CSF), MCP-1, RANTES, interleukin-3 (IL-3), supporting tumor survival. Chemotherapy, irradiation, and vascular destroying agents (such as combretastatin-A4-P) cause increased production of colony stimulating factor CSF1 and chemokines CCL2 (MCP-1) and CXCL12 (ligands for CCR2 and CXCR4 expressed on monocytes), which can initiate monocyte recruitment and TAM accumulation in the tumor [62]. Thus, restoration of p53 function in tumor cells affected by cytostatic agents led to an increase in the production of the main chemoattractant for monocyte-macrophage cells M-CSF and IL-15, chemokines CCL2 and CXCL1, expression of adhesion molecules intercellular adhesion molecules (ICAM1) and VCAM1 [63]. In mouse mammary tumors, chemotherapy increased the expression of CSF1 by tumor cells, which then attracted a large number of CSF1R-expressing monocytes [64]. Recruitment of monocytes into the tumor sites during cytostatic treatment is realized through CCR2/CCL2-dependent mechanism and plays a negative role regarding clinical outcomes [57]. At the same time, the knockout of the CCR2 gene was accompanied by a better response to doxorubicin or cisplatin based chemotherapy with [57].

Migration blockade of monocytes using the combination of anti-CCL2 (carlumab, CNTO 888) with conventional chemotherapy (docetaxel, oxaliplatin and irinotecan plus folinic acid and 5-fluorouracil (5-FU)) results in an increase of the antitumor response in prostate and pancreatic cancers [65, 66]. In the model of breast cancer, interruption of anti-CCL2 therapy was associated with an increase in the output of monocytes from the bone marrow, increased mobilization of tumor cells from the primary node, an increase in their infiltration in the areas of metastases, and enhanced angiogenesis in the tumor tissue under the influence of interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) [67, 68].

Different cytostatic drugs are proposed to be associated with various specific TAM subpopulations differentiated from monocytes *in situ*. Thus, in the MDA-MB435 human breast carcinoma cell line, the use of paclitaxel in the composition of paclitaxel + albumin was accompanied by a more pronounced tumor infiltration of CD45 + CD169 + macrophages than in samples without the use of cytostatic drug. Flow cytometry confirmed a significant increase in the F4/80⁺ macrophage population in MDA-MB-435 tumors sensitive to paclitaxel, but not in resistant MDA-MB-435R tumors [69]. On the other hand, cyclophosphamide stimulated an increase in M2-like CD206⁺ macrophages in mice [59].

Chemotherapy affects the functional polarization of monocytes and macrophages. The functional polarization of monocytes/macrophages can be determined or altered by exposure to cytostatics. Chemotherapy was shown to be accompanied by the appearance of TAM producing interleukin-34 (IL-34) that led to immunosuppression [70]. *In vitro*, treatment of human monocytes with cisplatin led to an increase in their ability to activate CD4⁺ T-responsive cells. This stimulation was based on the increased production of interferon beta (IFN- β) [71].

Cisplatin caused the increased antigen-presenting function of peritoneal macrophages through the release of IL-1, IL-6, IL-8 and tumor necrosis factor alpha (TNF- α) [72]. In various mouse cancer models, oxaliplatin increased the number of TAMs and neutrophils generating reactive oxygen species that mediated DNA damage and apoptosis [71]. In addition, experiments on cell lines and in mouse models showed that paclitaxel can reprogram pro-tumor (M2) macrophages into antitumor (M1) pathways in a TLR4-dependent way [73]. As well docetaxel caused the depletion of antitumor M2-like and activation of antitumor M1-like TAMs, which were able to enhance the cytotoxic T-cell response in mammary tumors 4T1-Neu in mice [74]. Doxorubicin in combination with immunotherapy led to an increase in M1-associated molecules (CD40, CD80, CD86, MHC II, IFN- γ , TNF- α , IL-12) and decrease in M2-associated molecules (IL-4R α , B7-H1, IL-4, IL-10) [75].

Cytostatic therapy modulates epigenetic profile of macrophages. To date, only few stud-

ies on the use of inhibitors of enzymes regulating the epigenetic profile of TAMs are available. In mice treated with TMP195, inhibitor of HDAC, was shown to induce TAM antitumor polarization. The combination of TMP195 and carboplatin/paclitaxel enhanced the antitumor effect compared to therapy with a cytostatic agent alone [43]. The combination of other HDAC inhibitor vorinostat [suberoylanilide hydroxamic acid (SAHA)] and synthetic triterpenoid 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO-Me and CDDO-Ea) allowed TAMs to decrease tumor in mouse mammary models [76]. These studies suggest that HDAC inhibitors impact to TAMs mediated effective delay of tumor growth, thereby demonstrating a promising, novel drug combination for chemoprevention.

Thus, cytostatic agents are able to modulate the recruitment of monocytes into the tumor, their differentiation to specific TAM populations and their participation in adaptive antitumor immune response inducing by chemotherapy. Such modulation can dramatically affect the development of tumor, thereby contributing to the clinical manifestation of disease (good or poor outcome). Therefore, it is actual to determine the regimens of cytostatic therapy inducing antitumor activity of immune system to increase cooperative therapeutic effect. It is important to elaborate such cytostatic therapy regimen that combines tumor cytorreduction effects and regulation of the functional state of TAMs to increase antitumor response.

TAM FUNCTIONAL POLARIZATION: PROGNOSTIC VALUE AND CONTRIBUTION TO THERAPY RESPONSE

There are numerous reports pointing to prognostic value of TAM counts in tumor regarding outcomes in cancer patients. These data are rather controversial because of different functional status of TAM in each patient depending on macrophage polarization and activity. The massive infiltration of CD68⁺ and CD163⁺ TAM in esophageal cancer patients treated with a combination of cisplatin, 5-FU and doxorubicin was significantly associated with tumor size, lymphogenous and hematogenous metastasis, and poor prognosis [77]. However, in gastric and colorectal cancer patients treated with 5-FU, a large amount of TAM correlated with increased survival [78, 79]. In patients with pancreatic adenocarcinoma, who received gemcitabine, a high level of CD68⁺ TAM was associated with a better prognosis [80].

There are several mechanisms by which TAM can increase tumor chemoresistance. Macrophages expressing cathepsin are the cause of drug resistance, because they protect against paclitaxel, etoposide and doxorubicin-induced tumor cell death [58–60]. Studies of Nakasone *et al.* [58] showed that the induction of resistance to doxorubicin was mediated by macrophages producing metalloprotease 9 (MMP9) during therapy. Macrophage-produced MMP9 reduced the blood vessel permeability, thereby limiting the delivery of drugs to the tumor. CD206⁺ TIE2^{high} CXCR4^{high} TAMs were accumulated around blood vessels in tumors

after treatment with cyclophosphamide, paclitaxel and doxorubicin, promoting tumor revascularization and relapse, partly due to VEGF production [69]. These results showed that after exposure to chemotherapy, macrophages were able to maintain drug resistance of tumor cells.

On the other hand, stimulation of angiogenesis may be accompanied by opposite effects. Thus, CD206⁺ macrophages contributed to the increase in the number of vessels that was accompanied by the best therapeutic response to doxorubicin [81]. The authors reported that the increased number of vessels was associated with the increased delivery of anticancer drugs to tumor cells and the increased number of targets for cytostatic effects. These results can be regarded as a manifestation of synergistic effects of TAMs and cytostatic treatment. In addition, the use of doxorubicin stimulated the accumulation of CD11b⁺ F4/80⁺ Gr-1(Ly6C/Ly6G)⁺ cells involved in antigen presentation and induction of antitumor T-cell immunity, thus correlating with a decreased tumor growth [82].

CONCLUSION

Monocytes are considered as a plastic and functional resource to create the population of tumor associated macrophages. Cytostatic therapy was reported to increase the recruitment of monocytes into tumor and the amount of TAMs and significantly affect the function of monocytes/macrophages. The functional polarization of monocytes/macrophages was shown to be modulated by cytostatic agents towards inducing tumor-supporting or tumor-inhibiting activities. The high functional plasticity of macrophages allow regulate their activity by different factors, especially, modification of TAM epigenetic profile. Combination of cytostatic therapy with specific macrophage regulatory agents targeted to pathogenic molecules and events, contributing markedly to tumor progression, is expected to improve treatment results. Combination of cytostatic therapy regimens with immunotherapy is considered to be promising from the point of increased antitumor efficacy.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

1. Ricci MS. Chemotherapeutic approaches for targeting cell death pathways. *Oncologist* 2006; **11**: 342–57.
2. Zitvogel L, Kepp O, Kroemer G. Immune parameters affecting the efficacy of chemotherapeutic regimens. *Nat Rev Clin Oncol* 2011; **8**: 151–60.
3. Coffelt SB, de Visser KE. Immune-mediated mechanisms influencing the efficacy of anticancer therapies. *Trends Immunol* 2015; **36**: 198–216.
4. Laoui D, Van Overmeire E, Van Ginderachter JA. Unsuspected allies: Chemotherapy teams up with immunity to fight cancer. *Eur J Immunol* 2013; **43**: 2538–42.

5. Kroemer G, Galluzzi L, Zitvogel L. Immunological effects of chemotherapy in spontaneous breast cancers. *Oncoimmunology* 2013; **2**: 41–4.
6. Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. *Nat Rev Immunol* 2005; **5**: 953–64.
7. Wynn TA, Chawla A, Pollard JW. Macrophage biology in development, homeostasis and disease. *Nature* 2013; **496**: 445–55.
8. Cherdyntseva NV, Mitrofanova IV, Buldakov MA, *et al.* Macrophages and tumor progression: on the way to macrophage-specific therapy. *Bull Sib Med* 2017; **16**: 61–74.
9. Ngambenjawong C, Gustafson HH, Pun SH, *et al.* Progress in tumor-associated macrophage (TAM)-targeted therapeutics. *Adv Drug Deliv Rev* 2017; **114**: 206–21.
10. Ponzoni M, Pastorino F, Di Paolo D, *et al.* Targeting macrophages as a potential therapeutic intervention: Impact on inflammatory diseases and cancer. *Int J Mol Sci* 2018; **19**: 1953.
11. Bercovici N, Guérin MV, Trautmann A, *et al.* The Remarkable Plasticity of Macrophages: A Chance to Fight Cancer. *Front Immunol* 2019; **10**: 1–9.
12. Röszer T. Understanding the biology of self-renewing macrophages. *Cells* 2018; **7**: 103.
13. Ginhoux F, Jung S. Monocytes and macrophages: Developmental pathways and tissue homeostasis. *Nat Rev Immunol* 2014; **14**: 392–404.
14. Varol C, Mildner A, Jung S. Macrophages: development and tissue specialization. *Annu Rev Immunol* 2015; **33**: 643–75.
15. Laurenti E, Göttgens B. From haematopoietic stem cells to complex differentiation landscapes. *Nature* 2016; **25**: 289–313.
16. Paul F, Arkin Y, Giladi A, *et al.* Transcriptional heterogeneity and lineage commitment in myeloid progenitors. *Cell* 2015; **163**: 1663–77.
17. Movahedi K, Laoui D, Gysemans C, *et al.* Different tumor microenvironments contain functionally distinct subsets of macrophages derived from Ly6C(high) monocytes. *Cancer Res* 2010; **70**: 5728–39.
18. Cortez-Retamozo V, Etzrodt M, Newton A, *et al.* Origins of tumor-associated macrophages and neutrophils. *Proc Natl Acad Sci* 2012; **109**: 2491–6.
19. Sawanobori Y, Ueha S, Kurachi M, *et al.* Chemokine-mediated rapid turnover of myeloid-derived suppressor cells in tumor-bearing mice. *Blood* 2008; **111**: 5457–66.
20. Yoshimura T. The chemokine MCP-1 (CCL2) in the host interaction with cancer: A foe or ally? *Cell Mol Immunol* 2018; **15**: 335–45.
21. Franklin RA, Liao W, Sarkar A, *et al.* The cellular and molecular origin of tumor-associated macrophages. *Science* 2014; **344**: 921–5.
22. Pucci F, Garriss C, Lai CP, *et al.* SCS macrophages suppress melanoma by restricting. *Science* 2016; **352**: 242–6.
23. Yang X, Wang X, Liu D, *et al.* Epigenetic regulation of macrophage polarization by DNA methyltransferase 3b. *Mol Endocrinol* 2014; **28**: 565–74.
24. Cheng C, Huang C, Ma TT, *et al.* SOCS1 hypermethylation mediated by DNMT1 is associated with lipopolysaccharide-induced inflammatory cytokines in macrophages. *Toxicol Lett* 2014; **225**: 488–97.
25. Zhang Q, Zhao K, Shen Q, *et al.* Tet2 is required to resolve inflammation by recruiting Hdac2 to specifically repress IL-6. *Nature* 2015; **525**: 389–93.
26. Stender JD, Pascual G, Liu W, *et al.* Control of pro-inflammatory gene programs by regulated trimethylation and demethylation of histone H4K20. *Mol Cell* 2012; **48**: 28–38.
27. Schliebe C, Flynn EK, Vilagos B, *et al.* The methyltransferase Setdb2 mediates virus-induced susceptibility to bacterial superinfection. *Nat Immunol* 2015; **16**: 67–74.
28. Fan Z, Li J, Li P, *et al.* Protein arginine methyltransferase 1 (PRMT1) represses MHC II transcription in macrophages by methylating CIITA. *Sci Rep* 2017; **7**: 1–9.
29. Kittan NA, Allen RM, Dhaliwal A, *et al.* Cytokine induced phenotypic and epigenetic signatures are key to establishing specific macrophage phenotypes. *PLoS One* 2013; **8**: 1–15.
30. Nguyen KD. Circadian gene Bmal1 regulates diurnal oscillations of Ly6C. *Science* 2013; **341**: 1483–8.
31. Liu Y, Zhang Q, Ding Y, *et al.* Histone lysine methyltransferase Ezh1 promotes TLR-triggered inflammatory cytokine production by suppressing Tollip. *J Immunol* 2015; **194**: 2838–46.
32. Xia M, Liu J, Wu X, *et al.* Histone methyltransferase ash1l suppresses interleukin-6 production and inflammatory autoimmune diseases by inducing the ubiquitin-editing enzyme A20. *Immunity* 2013; **39**: 470–81.
33. van Essen D, Zhu Y, Saccani S. A feed-forward circuit controlling inducible NF- κ B target gene activation by promoter histone demethylation. *Mol Cell* 2010; **39**: 750–60.
34. Zhu Y, van Essen D, Saccani S. Cell-type-specific control of enhancer activity by H3K9 trimethylation. *Mol Cell* 2012; **46**: 408–23.
35. Foster SL, Hargreaves DC, Medzhitov R. Gene-specific control of inflammation by TLR-induced chromatin modifications. *Nature* 2007; **447**: 972–8.
36. Satoh T, Takeuchi O, Vandenbon A, *et al.* The Jmjd3-Irf4 axis regulates M2 macrophage polarization and host responses against helminth infection. *Nat Immunol* 2010; **11**: 936–44.
37. Mounce BC, Mboko WP, Kanack AJ, *et al.* Primary macrophages rely on histone deacetylase 1 and 2 expression to induce type I interferon in response to gammaherpesvirus infection. *J Virol* 2014; **88**: 2268–78.
38. Chen X, Barozzi I, Termanini A, *et al.* Requirement for the histone deacetylase Hdac3 for the inflammatory gene expression program in macrophages. *Proc Natl Acad Sci* 2012; **109**: E2865–74.
39. Mullican SE, Gaddis CA, Alenghat T, *et al.* Histone deacetylase 3 is an epigenomic brake in macrophage alternative activation. *Genes Dev* 2011; **25**: 2480–8.
40. Yang Q, Wei J, Zhong L, *et al.* Cross talk between histone deacetylase 4 and stat6 in the transcriptional regulation of arginase 1 during mouse dendritic cell differentiation. *Mol Cell Biol* 2015; **35**: 63–75.
41. Kapellos TS, Iqbal AJ. Epigenetic control of macrophage polarisation and soluble mediator gene expression during inflammation. *Mediators Inflamm* 2016; **2016**: 6591703.
42. Nicodeme E, Jeffrey KL, Schaefer U, *et al.* Suppression of inflammation by a synthetic histone mimic. *Nature* 2010; **468**: 1119–23.
43. Guerriero JL, Sotayo A, Ponichtera HE, *et al.* Class IIa HDAC inhibition reduces breast tumours and metastases through anti-tumour macrophages. *Nature* 2017; **543**: 428–32.
44. Lobera M, Madauss KP, Pohlhaus DT, *et al.* Selective class IIa histone deacetylase inhibition via a nonchelating zinc-binding group. *Nat Chem Biol* 2013; **9**: 319–25.
45. Reichman H, Munitz A. Harnessing class II histone deacetylases in macrophages to combat breast cancer. *Cell Mol Immunol* 2017; **14**: 575–7.
46. Cassetta L, Pollard JW. Repolarizing macrophages improves breast cancer therapy. *Cell Res* 2017; **27**: 963–4.

47. Sainz B, Carron E, Vallespinós M, *et al.* Cancer stem cells and macrophages: implications in tumor biology and therapeutic strategies. *Mediators Inflamm* 2016; **2016**: 9012369.
48. Yang M, McKay D, Pollard JW, *et al.* Diverse functions of macrophages in different tumor microenvironments. *Cancer Res* 2018; **78**: 5492–503.
49. Gwak JM, Jang MH, Kim D II, *et al.* Prognostic value of tumor-associated macrophages according to histologic locations and hormone receptor status in breast cancer. *PLoS One* 2015; **10**: e0125728.
50. Buldakov M, Zavyalova M, Krakhmal N, *et al.* CD68+, but not stabilin-1+ tumor associated macrophages in gaps of ductal tumor structures negatively correlate with the lymphatic metastasis in human breast cancer. *Immunobiology* 2017; **222**: 31–8.
51. Mantovani A, Schioppa T, Porta C, *et al.* Role of tumor-associated macrophages in tumor progression and invasion. *Cancer Metastasis Rev* 2006; **25**: 315–322.
52. Sica A, Mantovani A. Macrophage plasticity and polarization: *in vivo* veritas. *J Clin Invest* 2012; **122**: 787–95.
53. Larionova I, Cherdyntseva N, Liu T, *et al.* Interaction of tumor-associated macrophages and cancer chemotherapy. *Oncoimmunology* 2019; **8**: 1–15.
54. Nazir T, Taha N, Islam A, *et al.* Monocytopenia; induction by vinorelbine, cisplatin and doxorubicin in breast, non-small cell lung and cervix cancer patients. *Int J Health Sci (Qassim)* 2016; **10**: 542–7.
55. Saeed L, Patnaik MM, Begna KH, *et al.* Prognostic relevance of lymphocytopenia, monocytopenia and lymphocyte-to-monocyte ratio in primary myelodysplastic syndromes: A single center experience in 889 patients. *Blood Cancer J* 2017; **7**: e550–6.
56. Ouyang W, Liu Y, Deng D, *et al.* The change in peripheral blood monocyte count: A predictor to make the management of chemotherapy-induced neutropenia. *J Cancer Res Ther* 2018; **14**: 565.
57. Nakasone ES, Askautrud HA, Kees T, *et al.* Imaging tumor-stroma interactions during chemotherapy reveals contributions of the microenvironment to resistance. *Cancer Cell* 2012; **21**: 488–503.
58. de Nardo DG, Brennan DJ, Rexhepaj E, *et al.* Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy. *Cancer Discov* 2011; **1**: 54–67.
59. Shree T, Olson OC, Elie BT, *et al.* Macrophages and cathepsin proteases blunt chemotherapeutic response in breast cancer. *Genes Dev* 2011; **25**: 2465–79.
60. Kioi M, Vogel H, Schultz G, *et al.* Inhibition of vasculogenesis, but not angiogenesis, prevents the recurrence of glioblastoma after irradiation in mice. *J Clin Invest* 2010; **120**: 694–705.
61. Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. *Immunity* 2019; **51**: 27–41.
62. Hughes R, Qian BZ, Rowan C, *et al.* Perivascular M2 macrophages stimulate tumor relapse after chemotherapy. *Cancer Res* 2015; **75**: 3479–91.
63. Xue W, Zender L, Miething C, *et al.* Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. *Mol Psychiatry* 2015; **20**: 1588–95.
64. de Palma M, Lewis CE. Macrophages limit chemotherapy. *Cancer Discov* 2011; **1**: 54–67.
65. Hu J, Kinn J, Zirakzadeh AA, *et al.* The effects of chemotherapeutic drugs on human monocyte-derived dendritic cell differentiation and antigen presentation. *Clin Exp Immunol* 2013; **172**: 490–9.
66. Loberg RD, Ying C, Craig M, *et al.* Targeting CCL2 with systemic delivery of neutralizing antibodies induces prostate cancer tumor regression *in vivo*. *Cancer Res* 2007; **67**: 9417–24.
67. Bonapace L, Coissieux MM, Wyckoff J, *et al.* Cessation of CCL2 inhibition accelerates breast cancer metastasis by promoting angiogenesis. *Nature* 2014; **515**: 130–3.
68. Patysheva MR, Stakheeva MN, Larionova IV, *et al.* Monocytes and cancer: promising role as a diagnostic marker and application in therapy. *Bull Sib Med* 2019; **18**: 60–75.
69. Hughes R, Qian BZ, Rowan C, *et al.* Perivascular M2 macrophages stimulate tumor relapse after chemotherapy. *Cancer Res* 2015; **75**: 3479–91.
70. Baghdadi M, Wada H, Nakanishi S, *et al.* Chemotherapy-induced IL34 enhances immunosuppression by tumor-associated macrophages and mediates survival of chemoresistant lung cancer cells. *Cancer Res* 2016; **76**: 6030–42.
71. Iida N, Dzutsev A, Stewart CA, *et al.* Commensal bacteria control cancer the tumor microenvironment. *Science* 2013; **342**: 967–71.
72. Singh RAK, Sodhi A. Antigen presentation by cisplatin-activated macrophages: Role of soluble factor(s) and second messengers. *Immunol Cell Biol* 1998; **76**: 513–9.
73. Wanderley CW, Colón DF, Luiz JPM, *et al.* Paclitaxel reduces tumor growth by reprogramming tumor-associated macrophages to an M1 profile in a TLR4-dependent manner. *Cancer Res* 2018; **78**: 5891–900.
74. Kodumudi KN, Woan K, Gilvary DL, *et al.* A novel chemoimmunomodulating property of docetaxel: Suppression of myeloid-derived suppressor cells in tumor bearers. *Clin Cancer Res* 2010; **16**: 4583–94.
75. Buhtoiarov IN, Sondel PM, Wigginton JM, *et al.* Anti-tumour synergy of cytotoxic chemotherapy and anti-CD40 plus CpG-ODN immunotherapy through repolarization of tumour-associated macrophages. *Immunology* 2011; **132**: 226–39.
76. Tran K, Risingsong R, Royce DB, *et al.* The combination of the histone deacetylase inhibitor vorinostat and synthetic triterpenoids reduces tumorigenesis in mouse models of cancer. *Carcinogenesis* 2013; **34**: 199–210.
77. Sugimura K, Miyata H, Tanaka K, *et al.* High infiltration of tumor-associated macrophages is associated with a poor response to chemotherapy and poor prognosis of patients undergoing neoadjuvant chemotherapy for esophageal cancer. *J Surg Oncol* 2015; **111**: 752–9.
78. Wang B, Xu D, Yu X, *et al.* Association of intra-tumoral infiltrating macrophages and regulatory T cells is an independent prognostic factor in gastric cancer after radical resection. *Ann Surg Oncol* 2011; **18**: 2585–93.
79. Malesci A, Bianchi P, Celesti G, *et al.* Tumor-associated macrophages and response to 5-fluorouracil adjuvant therapy in stage III colorectal cancer. *Oncoimmunology* 2017; **6**: 1–11.
80. Di Caro G, Cortese N, Castino GF, *et al.* Dual prognostic significance of tumour-Associated macrophages in human pancreatic adenocarcinoma treated or untreated with chemotherapy. *Gut* 2015; **65**: 1710–20.
81. Litviakov N, Tsyganov M, Larionova I, *et al.* Expression of M2 macrophage markers YKL-39 and CCL18 in breast cancer is associated with the effect of neoadjuvant chemotherapy. *Cancer Chemother Pharmacol* 2018; **82**: 99–109.
82. Hannesdóttir L, Tymoszyk P, Parajuli N, *et al.* Lapatinib and doxorubicin enhance the Stat1-dependent antitumor immune response. *Eur J Immunol* 2013; **43**: 2718–29.