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Article

Chemokines are Underestimated in Preventing the Metastasizing and the Immune Elimination of Ovarian Cancer

Petra L.M. Zusterzeel[1] and Ruurd Torensma[2*]

[1] *Department of Obstetrics and Gynecology, Radboudumc, Nijmegen, Netherlands*, e-mail: Petra.Zusterzeel@radboudumc.nl

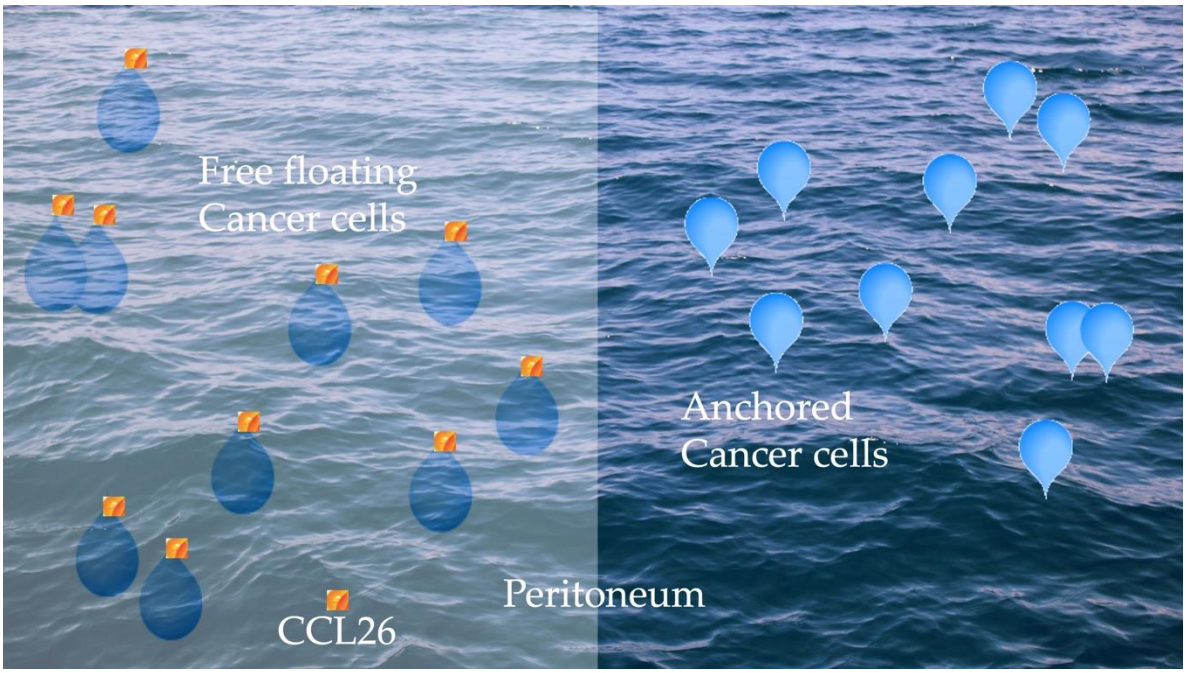
[2]*Department of Tumorimmunology, Radboud Molecular Life Sciences, Radboudumc, Nijmegen, Netherlands*, e-mail: Ruurd.Torensma@radboudumc.nl

* Corresponding author: Ruurd Torensma, Department of Tumorimmunology, Radboud Molecular Life Sciences, Radboudumc, GeertGrooteplein 26, 6525GA Nijmegen, Netherlands

e-mail: Ruurd.Torensma@radboudumc.nl

Short title: Chemokines: influencers on ovarian cancer

Graphical Abstract



1. Abstract

Nowadays the positive immune involvement in the eradication of tumor cells is assigned to the adaptive immune response. By awakening of in vivo responding T cells that are suppressed by the tumor and prevents immunological cure of the cancer. The adaptive immune response is a complex of different cells and protein molecules. Normally activated T cells are well-ordered by several late occurring inhibitors to contain the response to the unknown invaders and spare the normal cells. The tumor strengthens this inhibitory response to escape from immune elimination. Immunotherapy is to unleash the full capacity of the adaptive immune system by blocking this inhibitor response by monoclonal antibodies but with the potential drawback of autoimmune phenomena. Seen the success of the immunotherapy another feature of the immune system is overlooked. Cytokines and chemokines became in oblivion after their suspected necrosis of the tumor (TNF) did not fulfil their initial hope. When patients seek help for their complaints the ovarian cancer is in most cases already metastasized to the peritoneum and omentum. Here, we show that on the one hand chemokines

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produced by Th2, CD8 and NK cells inhibit cancer spreading and thus leads to a better operability and thus better survival. On the other hand, chemokine receptors are expressed by the tumor that are a decoy by binding chemokines that normally should attract antigen cross-presenting dendritic cells, which start an adaptive T cell response.

Keywords: ovarian cancer metastasis, chemokines, cytoreductive surgery, Cytotoxic T cells, BDCA3 Dendritic cells.

1. Introduction

Several papers describe that the presence of cytotoxic T cells (CTL) in ovarian cancer tissue will prolong their survival [1-3]. Apparently, the tumor is an incentive for CTL's to enter the microenvironment but only the Ag specific will enter the tumor. They need an integrin (CD103) expressed on the surface to enter the tumor bed [4,5]. In ovarian cancer a few mutations are found. According to the tumor portal **94**% of the ovarian tumors (http://www.tumorportal.org/tumor_types?ttype=OV) show TP53 mutations/deletions. A deletion of TP53 will not lead to an abundant immune recognition. So, there are only a low number of specific CD8 T-cells that have a tremendous effect on survival. The question arises how these few CTLs are able to impede the overwhelming number of tumor cells. The majority of the CTL are in the stromal compartment of the tumor. If those CTL that were alerted by the tumor but cannot penetrate the tumor tissue attribute to the production of chemokines remains elusive. But the overshoot of chemokines that are found in the ascites and since the volume of ascites is several liters there should be large cell pool that produces them. The tumor expresses several chemokine receptors like CX_3CR_1 [6]. Here, we show that the tumor expresses chemokine receptors that by binding to chemokine CCL26 are unable to bind to membrane bound fractalkine reducing their metastasis. [7-13]. Less binding to the fractalkine bearing peritoneum and omentum will result in less tumor spots and thus a better operability. Better operability causes a longer survival [14-18]. Tumor cells express also the lymphotactin receptor XCR1 [19-21]. The chemokines XCL1 and XCL2 will bind to this decoy receptor. This results in less capacity to attract Ag cross-presenting dendritic cells (BDCA3) [22-24] and will diminish adaptive immunity.

2. Results and Discussion

Most patients with ovarian cancer that present themselves are diagnosed with advanced stage high-grade serous cancer and have a poor 5-year overall survival rate of just 30% [25,26]. Although in ovarian cancer, tumor-infiltrating $CD8^+$ T cells are found and linked with improved overall survival [2,27,28]. But this influx of immune cells does not prevent a cure of the disease. High grade serous ovarian cancer remains the deadliest cancer in gynecological cancers. In most cases TP 53 is mutated in ± 96% of the cases while 9 other genes are mutated at a very low abundancy [29]. This leads to a limited number of targets for a cytotoxic immune response, which is reflected by the low response of immunotherapy [30]. In those cases where the immunotherapy was functional a durable response was measured [31]. Immune histochemistry of ovarian cancer show a few CD8 cells in the tumor and even more in the stroma (Fig.1).

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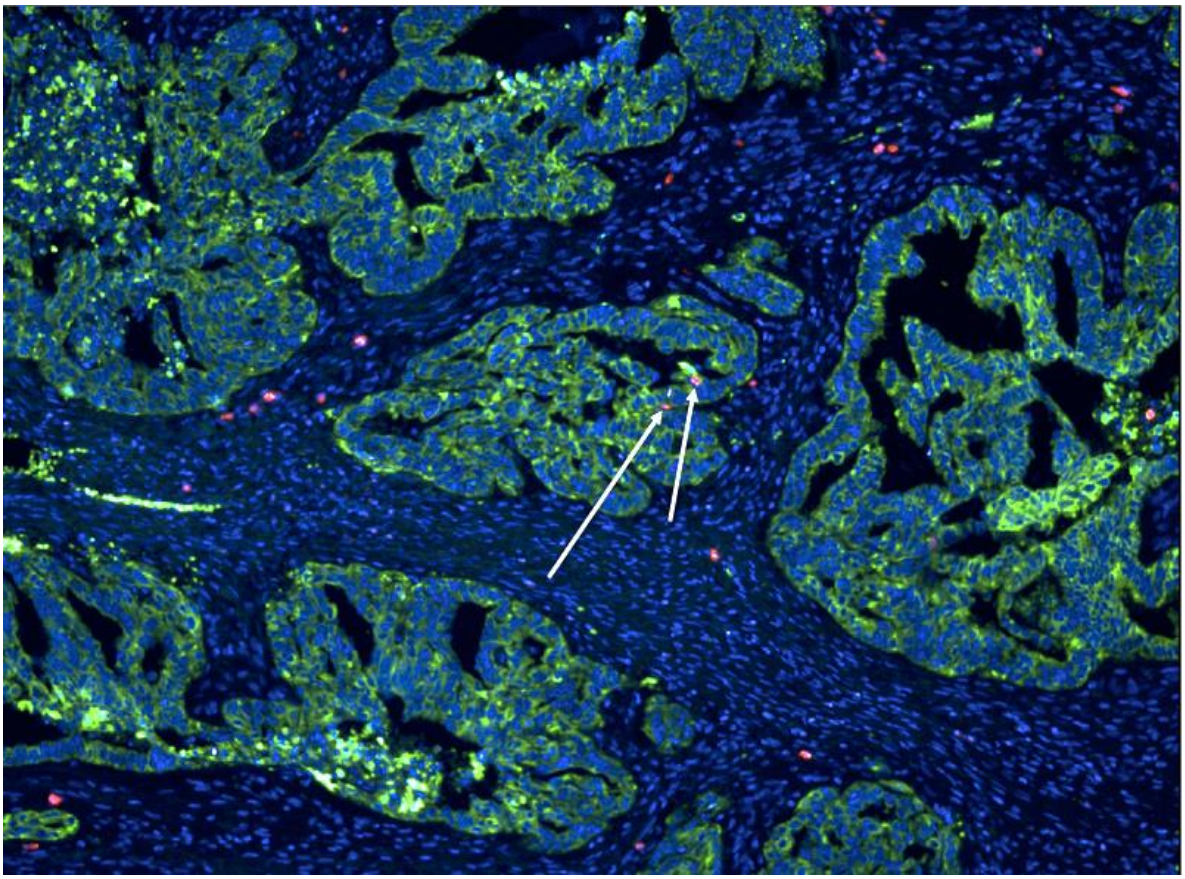

Fig 1. Expression of cytokeratin 7 (green) by tumor cells and cytotoxic T cells (red) (white arrows: cytotoxic T cells in tumor). The cells are colored with DAPI (blue).

Our previous results that Il-6 is found in ascitic fluid from malignant ovarian cancer [32] this was also reported by others [33]. Several other chemo/cytokines were described [34,35], BMP2 [36] soluble fractalkine [6,10,37]; CCL26 [12]; Lymphotactins: XCL1 and XCL2 [38,39] ; CCL2, CCL4, CCL5 [40]; G-CSF [41]; SDF-1 [42]. Th2 cells generate IL-4-/IL-13 that stimulate vascular endothelial cells and these cells abundantly produce CCL26 [12,43,44].

CCL26 appears an important chemokine in spreading of the tumor in the abdomen. If CCL26 is found in 1-10 liter ascites it indicates that CCL26 is produced in large quantities. Moreover, the production is enough to saturate the receptor and the remainder will appear in the ascites. Indeed, in several cases CCL26 is found in ascites (Table 1).

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Table 1. Expression of CCL26/eotaxin3 in ascites

Patient	CCL26 (pg/ml)	tumor type
56	0,0	serous 3c
57	0,0	serous 4
66	0,0	serous 3c
20	3,8	serous 3c
24	4,2	serous 3b
72	4,9	serous 4
47	9,7	serous 3c
71	10,0	adeno IV
58	10,0	serous 3c
21	26,4	serous 3c
75	29,3	serous 3c
30	53,7	serous 3c
73	61,5	clear cell 3c
37	84,8	serous 3c
23	88,3	serous 4
52	152,0	serous 3c
44,1	218,1	serous 3c

Three patients did not express CCL26. The other patients CCL26 blocked the fractalkine receptor and should lead to less seeding of the tumor cell on the peritoneum (Fig.2).

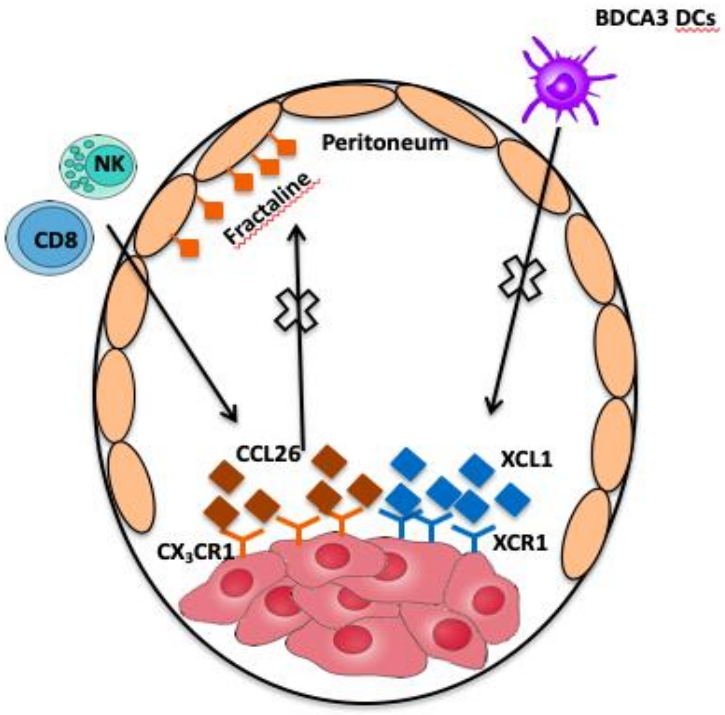

Fig.2. The expression of chemokines and their receptors

The fractalkine receptor CX_3CR1 is expressed on tumor cells allowing the tumor cells to bind to cell bound fractalkine that is present on mesothelial cells of the peritoneum and omentum. Indeed,

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spreading of tumor nests is different for individual patients as reported during surgical removal of the tumor. Patients with a better operability survive longer [17 ,18,45-47].

CCL26 produced by NK and CD8 cells can bind to the CX_3CR1 receptor [12]. Moreover, activated T cells produce IL-4 and IL-13 that stimulate vascular endothelial cells to produce CCL26. The presence of these compounds should shed light on the spreading of the tumor on the peritoneum and omentum. So, the presence of CCL26 should diminish nesting of floating tumor cells and those patients should have a better operability. Since CCL26 is produced by NK and CD8 cells it could explain the better survival when CD8 cells are in the tumor. Thus, CCL26 reduces the docking places for tumor cells on the peritoneum and omentum.

When tumors show XCR1 expression and secreted XCL1 or XCL2 by NK cells, will be bound by the tumor causing lowering the level of the chemokines in the fluid phase and leading to less influx of BDCA3 dendritic cells in the tumor microenvironment. Initially we found a very low BDCA3 in cells from ascites [18], which made us search for the cause of this low influx . BDCA3 DCs express the chemokine receptor XCR1, which binds the XCL1/2 chemokines and penetrate the tumor and start an immune response. The putative XCR1 expression on tumors could lower the level of XCL1/2 in ascites. This could explain the differences of BDCA3 dendritic cells found in the cell fraction of ascites fluid [18].

3. Materials and Methods

Ascites was obtained from stage III and IV high-grade serous ovarian cancer patients before start of the treatment. The study was carried out in accordance with the guidelines and regulation of the Radboudumc. The protocol was approved by the "Commissie Mensgebonden Onderzoek" (CMO Arnhem- Nijmegen). All subjects gave informed consent in accordance with the Declaration of Helsinki. Some samples were obtained before written consent was needed. Ascites was considered as waste material and only oral informed consent was necessary. All patients gave this oral informed consent to help future patients and were aware that it was not for their own benefit but for research purposes.

The CCL26 ELISA was from **R&D Systems, Inc.** Minneapolis, USA. Monoclonal antibody to CD8 (345774) was from BD Pharmingen, Vianen, Netherlands.

4. Conclusions

Immunology comprises several cells and protein molecules to eliminate invading pathogens and inhibit the response after invading pathogen is eradicated. Nowadays much effort in cancer treatment is the use of inhibition by monoclonal antibodies to membrane proteins that normally keep the immune system in check. Although much success is gathered it uses only one entity of the immune system. To expand the armament to Cancer also the other entities of the immune system should be exploited. Here, we highlighted the chemokines as influencers of cancer growth. By multivariate analysis of clinical data, cyto/chemokine levels, B- and T-cells, and the myeloid branch of the immune system, the important targets for each patient should be revealed leading to a better individualized treatment.

Author Contributions: P.Z. collected the specimen and assigned the diagnosis; RT designed the study and wrote the paper, both were involved in obtaining the data.

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Conflicts of Interest: The authors declare no conflict of interest.

References

1. Webb, J.R.; Wick, D.A.; Nielsen, J.S.; Tran, E.; Milne, K.; McMurtrie, E.; Nelson, B.H. Profound elevation of cd8+ t cells expressing the intraepithelial lymphocyte marker cd103 (alphae/beta7 integrin) in high-grade serous ovarian cancer. *Gynecol. Oncol.* **2010**, *118*, 228-236.
2. Sato, E.; Olson, S.H.; Ahn, J.; Bundy, B.; Nishikawa, H.; Qian, F.; Jungbluth, A.A.; Frosina, D.; Gnjatic, S.; Ambrosone, C., *et al.* Intraepithelial cd8+ tumor-infiltrating lymphocytes and a high cd8+/regulatory t cell ratio are associated with favorable prognosis in ovarian cancer. *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102*, 18538-18543.
3. de Jong, R.A.; Leffers, N.; Boezen, H.M.; ten Hoor, K.A.; van der Zee, A.G.; Hollema, H.; Nijman, H.W. Presence of tumor-infiltrating lymphocytes is an independent prognostic factor in type i and ii endometrial cancer. *Gynecol. Oncol.* **2009**, *114*, 105-110.
4. Webb, J.R.; Milne, K.; Watson, P.; Deleeuw, R.J.; Nelson, B.H. Tumor-infiltrating lymphocytes expressing the tissue resident memory marker cd103 are associated with increased survival in high-grade serous ovarian cancer. *Clin. Cancer Res.* **2014**, *20*, 434-444.
5. Komdeur, F.L.; Wouters, M.C.; Workel, H.H.; Tijans, A.M.; Terwindt, A.L.; Brunekreeft, K.L.; Plat, A.; Klip, H.G.; Eggink, F.A.; Leffers, N., *et al.* Cd103+ intraepithelial t cells in high-grade serous ovarian cancer are phenotypically diverse tcralphabeta+ cd8alphabeta+ t cells that can be targeted for cancer immunotherapy. *Oncotarget* **2016**.
6. Kim, M.; Rooper, L.; Xie, J.; Kajdacsy-Balla, A.A.; Barbolina, M.V. Fractalkine receptor cx(3)cr1 is expressed in epithelial ovarian carcinoma cells and required for motility and adhesion to peritoneal mesothelial cells. *Mol. Cancer Res.* **2012**, *10*, 11-24.
7. Gurler Main, H.; Xie, J.; Muralidhar, G.G.; Elfituri, O.; Xu, H.; Kajdacsy-Balla, A.A.; Barbolina, M.V. Emergent role of the fractalkine axis in dissemination of peritoneal metastasis from epithelial ovarian carcinoma. *Oncogene* **2017**, *36*, 3025-3036.
8. Shah, R.; Hinkle, C.C.; Ferguson, J.F.; Mehta, N.N.; Li, M.; Qu, L.; Lu, Y.; Putt, M.E.; Ahima, R.S.; Reilly, M.P. Fractalkine is a novel human adipochemokine associated with type 2 diabetes. *Diabetes* **2011**, *60*, 1512-1518.
9. Polyak, A.; Ferenczi, S.; Denes, A.; Winkler, Z.; Kriszt, R.; Pinter-Kubler, B.; Kovacs, K.J. The fractalkine/cx3cr1 system is implicated in the development of metabolic visceral adipose tissue inflammation in obesity. *Brain. Behav. Immun.* **2014**, *38*, 25-35.
10. Xie, J.; Gurler, H.; Burdette, J.; Barbolina, M. Cx3cr1, a fractalkine receptor, can regulate peritoneal dissemination of epithelial ovarian cancer cells. *Cancer Res.* **2013**, *73*, B72.
11. El-Shazly, A.E.; Doloriert, H.C.; Bisig, B.; Lefebvre, P.P.; Delvenne, P.; Jacobs, N. Novel cooperation between cx3cl1 and ccl26 inducing nk cell chemotaxis via cx3cr1: A possible mechanism for nk cell infiltration of the allergic nasal tissue. *Clin. Exp. Allergy* **2013**, *43*, 322-331.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 June 2019 doi:10.20944/preprints201906.0079.v1

12. Nakayama, T.; Watanabe, Y.; Oiso, N.; Higuchi, T.; Shigeta, A.; Mizuguchi, N.; Katou, F.; Hashimoto, K.; Kawada, A.; Yoshie, O. Eotaxin-3/cc chemokine ligand 26 is a functional ligand for cx3cr1. *J. Immunol.* **2010**, *185*, 6472-6479.
13. Nieman, K.M.; Kenny, H.A.; Penicka, C.V.; Ladanyi, A.; Buell-Gutbrod, R.; Zillhardt, M.R.; Romero, I.L.; Carey, M.S.; Mills, G.B.; Hotamisligil, G.S., *et al.* Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. *Nat. Med.* **2011**, *17*, 1498-1503.
14. Aletti, G.D.; Dowdy, S.C.; Podratz, K.C.; Cliby, W.A. Analysis of factors impacting operability in stage iv ovarian cancer: Rationale use of a triage system. *Gynecol. Oncol.* **2007**, *105*, 84-89.
15. Vergote, I.; van Gorp, T.; Amant, F.; Leunen, K.; Neven, P.; Berteloot, P. Timing of debulking surgery in advanced ovarian cancer. *Int. J. Gynecol. Cancer* **2008**, *18 Suppl 1*, 11-19.
16. Grabowski, J.P.; Harter, P.; Heitz, F.; Pujade-Lauraine, E.; Reuss, A.; Kristensen, G.; Ray-Coquard, I.; Heitz, J.; Traut, A.; Pfisterer, J., *et al.* Operability and chemotherapy responsiveness in advanced low-grade serous ovarian cancer. An analysis of the ago study group metadatabase. *Gynecol. Oncol.* **2016**, *140*, 457-462.
17. Torres, D.; Wang, C.; Kumar, A.; Bakkum-Gamez, J.N.; Weaver, A.L.; McGree, M.E.; Konecny, G.E.; Goode, E.L.; Cliby, W.A. Factors that influence survival in high-grade serous ovarian cancer: A complex relationship between molecular subtype, disease dissemination, and operability. *Gynecol. Oncol.* **2018**, *150*, 227-232.
18. Wefers, C.; Duiveman-de Boer, T.; Yigit, R.; Zusterzeel, P.L.M.; van Altena, A.M.; Massuger, L.; De Vries, I.J.M. Survival of ovarian cancer patients is independent of the presence of dc and t cell subsets in ascites. *Front Immunol* **2018**, *9*, 3156.
19. Khurram, S.A.; Whawell, S.A.; Bingle, L.; Murdoch, C.; McCabe, B.M.; Farthing, P.M. Functional expression of the chemokine receptor xcr1 on oral epithelial cells. *J. Pathol.* **2010**, *221*, 153-163.
20. Maru, S.V.; Holloway, K.A.; Flynn, G.; Lancashire, C.L.; Loughlin, A.J.; Male, D.K.; Romero, I.A. Chemokine production and chemokine receptor expression by human glioma cells: Role of cxcl10 in tumour cell proliferation. *J. Neuroimmunol.* **2008**, *199*, 35-45.
21. Kim, M.; Rooper, L.; Xie, J.; Rayahin, J.; Burdette, J.E.; Kajdacsy-Balla, A.A.; Barbolina, M.V. The lymphotactin receptor is expressed in epithelial ovarian carcinoma and contributes to cell migration and proliferation. *Mol. Cancer Res.* **2012**, *10*, 1419-1429.
22. Bachem, A.; Guttler, S.; Hartung, E.; Ebstein, F.; Schaefer, M.; Tannert, A.; Salama, A.; Movassaghi, K.; Opitz, C.; Mages, H.W., *et al.* Superior antigen cross-presentation and xcr1 expression define human cd11c+cd141+ cells as homologues of mouse cd8+ dendritic cells. *J. Exp. Med.* **2010**, *207*, 1273-1281.
23. Crozat, K.; Guiton, R.; Contreras, V.; Feuillet, V.; Dutertre, C.A.; Ventre, E.; Vu Manh, T.P.; Baranek, T.; Storset, A.K.; Marvel, J., *et al.* The xc chemokine receptor 1 is a conserved selective marker of mammalian cells homologous to mouse cd8alpha+ dendritic cells. *J. Exp. Med.* **2010**, *207*, 1283-1292.
24. Sehgal, K.; Ragheb, R.; Fahmy, T.M.; Dhodapkar, M.V.; Dhodapkar, K.M. Nanoparticle-mediated combinatorial targeting of multiple human dendritic cell (dc) subsets leads to enhanced t cell activation via il-15-dependent dc crosstalk. *J. Immunol.* **2014**, *193*, 2297-2305.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 June 2019 doi:10.20944/preprints201906.0079.v1

25. Salani, R.; Backes, F.J.; Fung, M.F.; Holschneider, C.H.; Parker, L.P.; Bristow, R.E.; Goff, B.A. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of gynecologic oncologists recommendations. *Am. J. Obstet. Gynecol.* **2011**, *204*, 466-478.
26. Wright, J.D.; Chen, L.; Tergas, A.I.; Patankar, S.; Burke, W.M.; Hou, J.Y.; Neugut, A.I.; Ananth, C.V.; Hershman, D.L. Trends in relative survival for ovarian cancer from 1975 to 2011. *Obstet. Gynecol.* **2015**, *125*, 1345-1352.
27. Zhang, L.; Conejo-Garcia, J.R.; Katsaros, D.; Gimotty, P.A.; Massobrio, M.; Regnani, G.; Makrigiannakis, A.; Gray, H.; Schlienger, K.; Liebman, M.N., *et al.* Intratumoral t cells, recurrence, and survival in epithelial ovarian cancer. *N. Engl. J. Med.* **2003**, *348*, 203-213.
28. Milne, K.; Kobel, M.; Kalloger, S.E.; Barnes, R.O.; Gao, D.; Gilks, C.B.; Watson, P.H.; Nelson, B.H. Systematic analysis of immune infiltrates in high-grade serous ovarian cancer reveals cd20, foxp3 and tia-1 as positive prognostic factors. *PLoS ONE* **2009**, *4*, e6412.
29. Cancer Genome Atlas Research, N. Integrated genomic analyses of ovarian carcinoma. *Nature* **2011**, *474*, 609-615.
30. Mills, K.; Fuh, K. Recent advances in understanding, diagnosing, and treating ovarian cancer. *F1000Res* **2017**, *6*, 84.
31. Varga, A.; Piha-Paul, S.; Ott, P.A.; Mehnert, J.M.; Berton-Rigaud, D.; Morosky, A.; Yang, P.; Ruman, J.; Matei, D. Pembrolizumab in patients with programmed death ligand 1-positive advanced ovarian cancer: Analysis of keynote-028. *Gynecol. Oncol.* **2019**, *152*, 243-250.
32. Yigit, R.; Figdor, C.G.; Zusterzeel, P.L.M.; Pots, J.M.; Torensma, R.; Massuger, L.F.A.G. Cytokine expression profiles in ovarian cancer related ascites. *Eur. J. Cancer* **2011**, *47*, 1883-1889.
33. Wouters, M.C.A.; Dijkgraaf, E.M.; Kuijjer, M.L.; Jordanova, E.S.; Hollema, H.; Welters, M.J.P.; van der Hoeven, J.J.M.; Daemen, T.; Kroep, J.R.; Nijman, H.W., *et al.* Interleukin-6 receptor and its ligand interleukin-6 are opposite markers for survival and infiltration with mature myeloid cells in ovarian cancer. *OncoImmunology* **2014**, *3*, e962397.
34. Bowtell, D.D.; Bohm, S.; Ahmed, A.A.; Aspuria, P.J.; Bast, R.C., Jr.; Beral, V.; Berek, J.S.; Birrer, M.J.; Blagden, S.; Bookman, M.A., *et al.* Rethinking ovarian cancer ii: Reducing mortality from high-grade serous ovarian cancer. *Nat. Rev. Cancer* **2015**, *15*, 668-679.
35. Lambeck, A.J.; Crijns, A.P.; Leffers, N.; Sluiter, W.J.; ten Hoor, K.A.; Braid, M.; van der Zee, A.G.; Daemen, T.; Nijman, H.W.; Kast, W.M. Serum cytokine profiling as a diagnostic and prognostic tool in ovarian cancer: A potential role for interleukin 7. *Clinical cancer research : an official journal of the American Association for Cancer Research* **2007**, *13*, 2385-2391.
36. Choi, Y.J.; Ingram, P.N.; Yang, K.; Coffman, L.; Iyengar, M.; Bai, S.; Thomas, D.G.; Yoon, E.; Buckanovich, R.J. Identifying an ovarian cancer cell hierarchy regulated by bone morphogenetic protein 2. *Proc. Natl. Acad. Sci. U. S. A.* **2015**.
37. Muralidhar, G.G.; Barbolina, M.V. Chemokine receptors in epithelial ovarian cancer. *Int. J. Mol. Sci.* **2014**, *15*, 361-376.
38. Kroczek, R.A.; Henn, V. The role of xcr1 and its ligand xcl1 in antigen cross-presentation by murine and human dendritic cells. *Frontiers in Immunology* **2012**, *3*.
39. Cohen, C.A.; Shea, A.A.; Heffron, C.L.; Schmelz, E.M.; Roberts, P.C. The parity-associated microenvironmental niche in the omental fat band is refractory to ovarian cancer metastasis. *Cancer Prev Res (Phila)* **2013**, *6*, 1182-1193.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 10 June 2019 doi:10.20944/preprints201906.0079.v1

40. Zsiros, E.; Duttagupta, P.; Dangaj, D.; Li, H.; Frank, R.; Garrabrant, T.; Hagemann, I.S.; Levine, B.L.; June, C.H.; Zhang, L., *et al.* The ovarian cancer chemokine landscape is conducive to homing of vaccine-primed and cd3/cd28-costimulated t cells prepared for adoptive therapy. *Clin. Cancer Res.* **2015**, *21*, 2840-2850.
41. Welte, T.; Rosen, J.M.; Zhang, X.H. Fatal attraction: Tics and mdscs. *Cell Cycle* **2016**, 1-3.
42. Pinho Mde, F.; Hurtado, S.P.; El-Cheikh, M.C.; Rossi, M.I.; Dutra, H.S.; Borojevic, R. Myelopoiesis in the omentum of normal mice and during abdominal inflammatory processes. *Cell Tissue Res.* **2002**, *308*, 87-96.
43. Blanchard, C.; Durual, S.; Estienne, M.; Emami, S.; Vasseur, S.; Cuber, J.C. Eotaxin-3/ccl26 gene expression in intestinal epithelial cells is up-regulated by interleukin-4 and interleukin-13 via the signal transducer and activator of transcription 6. *Int. J. Biochem. Cell Biol.* **2005**, *37*, 2559-2573.
44. Ancuta, P.; Rao, R.; Moses, A.; Mehle, A.; Shaw, S.K.; Luscinskas, F.W.; Gabuzda, D. Fractalkine preferentially mediates arrest and migration of cd16+ monocytes. *J. Exp. Med.* **2003**, *197*, 1701-1707.
45. Vergote, I.; van Gorp, T.; Amant, F.; Neven, P.; Berteloot, P. Neoadjuvant chemotherapy for ovarian cancer. *Oncology (Williston Park, N.Y.)* **2005**, *19*, 1615-1622; discussion 1623-1630.
46. Aure, J.C.; Hoeg, K.; Kolstad, P. Clinical and histologic studies of ovarian carcinoma. Long-term follow-up of 990 cases. *Obstet. Gynecol.* **1971**, *37*, 1-9.
47. Griffiths, C.T.; Fuller, A.F. Intensive surgical and chemotherapeutic management of advanced ovarian cancer. *Surg. Clin. North Am.* **1978**, *58*, 131-142.