Emerging cytokine networks in osteosarcoma

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Osteosarcoma is the most prevalent primary bone cancer. Although it has a global impact of approximately 1 to 3 cases/million a year [1, 2], it represents approximately 44% of all primary bone tumours among people under the age of 20 [1, 3, 4], and is most common among males. Its incidence increases with age throughout childhood, peaking during the growth spurt in adolescence [2, 4].

Osteosarcoma arises from bone-forming stem cells (immature osteoid tissue) and is composed of malignant fusiform spindle cells [2]. It normally develops in areas of rapid bone growth, such as the distal femur and proximal tibia [5]. The most important prognostic factor is the presence of pulmonary metastases that, in most patients, are present in the diagnosis of the disease [1, 6].

The overall 5-year survival rate of patients with metastatic or relapsed osteosarcoma is around 20% [7] and despite several attempts at intensifying chemotherapy and employing new agents in clinical trials [8], it has remained practically unchanged over the past 30 years. Therefore it is necessary to
understand the natural history and biology of osteosarcoma in order to improve therapeutic approaches [9].

The etiopathophysiology of osteosarcoma is still unknown and the immune response to its development is very individual as well as variable [3]. Gene mutations in the retinoblastoma (RB1) are observed in approximately 50% of osteosarcoma cases and patients with hereditary retinoblastoma are twice as likely to develop the disease. Similarly, mutations in the p53 gene are detected in approximately 50% of these tumours, and germline mutations of p53 associated with the Li-Fraumeni syndrome are also linked to an increased risk of osteosarcoma [6].

The p53 is a tumour suppressor gene that encodes a transcription factor (p53) that is capable of regulating genes involved in the cell cycle, DNA repair, and apoptosis [10]. Likewise RB1, also known as a tumour suppressor gene, is an important regulator of G1 to S phase cell cycle transition and genetic changes involving RB1 are found in up to 70% of sporadic cases of osteosarcoma [11, 12]. Furthermore, epigenetic modifications (hypermethylation, hypomethylation, histone modification and microRNAs) are also related to the development of osteosarcoma [13, 14].

Although the hypermethylation of the RB1 gene is associated with tumorigenesis [15], there is no evidence linking RB1 gene silencing with osteosarcoma. Similarly, there is some incipient data on the epigenetic mechanisms involving the p53 gene. However, p53 pathway intermediates are susceptible to hypermethylation and can consequently affect the biological functions of p53 [14]. In addition, HIC1 (hypermethylated in cancer 1) has emerged as a candidate tumour suppressor gene that appears to modulate the p53-dependent DNA damage pathway [16]. However, a recent meta-analysis showed that p53 mutations can only be used as a parameter for the survival rate for osteosarcoma patients [17].

Numerous studies have reported that gene polymorphisms are also associated with osteosarcoma genesis and progression [13, 18]. A previous study that compared the genotype of 941 human cases of osteosarcoma identified three associated single nucleotide polymorphisms (SNP), including two located in gene deserts and one connected to the glutamate receptor metabotropic 4 (GRM4) gene [18], which plays a role in cAMP signalling and thus can be important for bone tumorigenesis [13]. Other studies related to SNPs have been linked to metabolic pathways that are important in the development of osteosarcoma, but these studies have a limited statistical power due to the small sample size [14].

Besides playing important roles in osteosarcoma pathogenesis and progression, cytokines are crucial in orchestrating the immune response to this type of cancer [19]. Compelling evidence has shown that the interaction of cytokines, chemokines, growth factors, and cancer cells form a network at the tumour site - known as tumour microenvironment - that is responsible for the progression or rejection of tumours [20]. The characterization of cytokine networks in the various types of cancer may yield important information for understanding the immune-related mechanisms of carcinogenesis, a knowledge that has potential application in cancer immunotherapy [13]. In light of this, the purpose of this review was to highlight the classic roles of cytokines in osteosarcoma, to describe the role of new players in the emerging cytokine network, and to discuss the therapeutic targets that encompass the complexity and implications of this network.

Cytokines and Osteosarcoma

Cytokines are signalling proteins that are released by a variety of cells in response to a range of stresses, including inflammation [21]. In the tumour microenvironment, cytokines stimulate the host response to control cellular stress and reduce cellular damage. The failure to address the stress injury can lead to persistent cytokine production and increased tissue destruction. Therefore, host reactions to cellular stress can affect several stages of cancer formation and progression [21, 22]. A deep understanding of the complex cytokine interplay in oncogenesis may have prognostic significance for the course and progression of osteosarcoma. Special emphasis must be placed on the role of emerging cytokine networks in immunoregulatory and coordinating functions [3].

Bone destruction and pathological bone formation are crucial features in the natural course of osteosarcoma [23], which implies that several cytokines must be involved in the pathogenesis of these tumours. While the effects of autocrine and paracrine signalling of some cytokines and other growth factors on established osteosarcoma cell lines have been demonstrated [24, 25, 26, 27], knowledge of the cytokine expression in osteosarcoma remains limited, and little is known about the contribution of cytokines to osteosarcoma progression [9].

Classical cytokines in osteosarcoma: An update

Interleukin-6 (IL-6)

IL-6 is a pro-inflammatory cytokine that was first described regarding its role in the maturation of B cells [28]. IL-6 signals through the receptor IL-6R that induces
conformational changes in the gp130 subunit, activating the janus kinase (JAK) and finally, the phosphorylation of signal transducer and activator of transcription 3 (STAT3) [59]. This signalling promotes proliferative and antiapoptotic functions, as observed in co-cultures of human mesenchymal stem cells and osteosarcoma cells. In these co-cultures, the neutralisation of IL-6 by specific antibodies or by STAT3 inhibition (with siRNA) reduced tumour progression [30]. In bone tumours, IL-6 contributes to bone degradation by promoting the differentiation of osteoclasts and the expression of proteins that act on bone resorption [31].

Several studies have demonstrated an increase in IL-6 expression in tissue from patients with osteosarcoma as compared to normal bone tissue. In addition, high expression levels of this cytokine are significantly correlated with the tumour stage [32, 33]. It has been previously shown that IL-6 induces the expression of the vascular endothelial growth factor (VEGF) in human osteosarcoma cells. Apoptosis signal-regulating kinase 1 (ASK1) and p38, which activate the activator protein 1 (AP-1) and subsequently contribute to angiogenesis, have been implicated in the pathways underlying VEGF induction by IL-6 [32].

In a murine model of osteosarcoma in the tibia, IL-6 has shown to contribute to metastasis by activating STAT3, given that the inhibition of JAK2 prevented pulmonary metastasis and increased animal survival [30]. In osteosarcoma cell cultures, the addition of IL-6 increased the expression of the intercellular adhesion molecule-1 (ICAM-1) as well as tumour cell migration [33].

**Vascular endothelial growth factor (VEGF)**

VEGF or VEGF-A is a member of a large family of growth factors composed of VEGF-B, VEGFC, VEGFD, and placental growth factor (PIGF:) [34]. VEGF signalling occurs through the binding to its receptor tyrosine kinases (RTKs), VEGFR-1, VEGFR-2, and VEGFR-2 [34]. VEGF role in inducing angiogenesis is noteworthy [34, 35]. In tumours, intracellular signalling is also possible through the binding with neuropilins (NRPs) and integrins [13].

Increased VEGF expression has shown to positively correlate with poor prognosis in various tumour types [36, 37]. Accordingly, several meta-analysis have shown that increased VEGF levels in patients are directly related to decreased survival and to tumour progression and consequently, to a poor prognosis [38, 39, 40]. Studies that have investigated molecular mechanisms involving VEGF showed the importance of regulating the VEGF/PI3K/AKT signalling pathway in the progression and development of osteosarcoma [41, 42].

**Transforming growth factor beta (TGFβ)**

TGFβ is a cytokine that belongs to a family composed of more than 30 molecules that are very close and encoded by different genes. TGFβ has three main isoforms: TGFβ1, TGFβ2, and TGFβ3 [45]. Their receptors, which are classified as type I, II or III, are expressed in most cell types, although the expression pattern is different for each tissue [44]. Activation of the TGFβ signal transduction begins after TGFβ binding to the type II receptor (TGFβ RI) and the subsequent binding of the type I receptors (TGFβRI) that phosphorylate SMAD2 and SMAD3, and translocate SMAD4 to the nucleus. Thereby, SMAD4 binds to the promoters of target genes and promotes transcription [43]. TGFβ signalling pathway results in different events of pleiotropic functions that regulate cell proliferation and differentiation, apoptosis, motility and invasion, extracellular matrix production, angiogenesis, and immune response [43].

In human cancers, TGFβ plays a dual role. In the early stages of carcinogenesis, TGFβ acts as tumour suppressor and its functions include inhibition of cell proliferation, induction of apoptosis, and inhibition of cell immortalisation [45, 46]. In later stages, TGFβ promotes metastasis by inducing epithelial-mesenchymal transition (EMT) and promoting cell adhesion, migration, invasion, and chemotaxis. These functions are especially observed in aggressive and invasive tumours [45, 46]. As regard to osteosarcoma, an in vitro study showed that tumour cells secrete TGFβ by activation of the TGFβ/SMAD-2/-3 signalling pathway. Mesenchymal stem cells, which are maintained in an undifferentiated state, have shown to produce high levels of pro-tumour cytokines, such as IL-6 and VEGF [47]. Other studies have shown that high TGFβ mRNA levels in tumour cells are associated with aggressive behaviour as well as with lung metastasis [48]. Significant increased activation of SMAD3 signalling cascades and increased amounts of TGFβ1 in the serum of patients at high risk of developing pulmonary metastasis have also been observed [46]. Furthermore, TGFβ gene polymorphism has been identified in the serum of patients with metastatic osteosarcoma [49]. Conversely, the overexpression of SMAD7 (SMAD signalling pathway inhibitor-2/-4) has been shown to decrease the capacity of primary osteosarcoma to develop pulmonary metastasis [46].

**Interferon (IFN)**

IFN are pro-inflammatory cytokines that form a large family subdivided into 3 categories: type I, II, and III [50]. Type I IFN comprises more than 20 members expressed in almost all cell types, the main ones being IFN-α and IFN-β. By binding to the receptor formed by IFNaR1 and IFNaR2, its signalling pathway culminates in the induction of
IFN-α is the sole representative of type II IFN. Upon binding to the receptor composed of IFNGR1 and IFNGR2, it activates JAK1 and JAK2 kinase, leading to STAT1 dimerization. Recently, a new family - type III IFN - was described, consisting of IFN-λ1, IFN-λ2, IFN-λ3 (also known as IL-29, IL-28A and IL-28B, respectively). The receptor of this family is expressed in a few cells and consists of the dimer IFNA-R1 and IL-10R2, which, upon stimulation, leads to STAT-1 and STAT-2 activation.

IFN-α has an anti-tumorigenic effect by activating innate immune cells such as macrophages and natural killer (NK) cells and also presents antiangiogenic properties. IFN-γ plays a controversial role since it has an antitumour activity by recruiting and activating cells of the immune system, leading to direct inhibition of tumour progression, and a pro-tumour activity that induces tumour cell proliferation and antiapoptotic signals by decreasing the cellular immune response mediated by NK and cytotoxic T cells.

In vitro studies with human osteosarcoma cells have shown that IFN-α was able to increase the autophagy and apoptosis mediated by cisplatin, and to suppress cell invasion. Similar results have been demonstrated by another study, in which IFN-λ1 inhibited tumour invasion and increased autophagy in a dose-dependent manner.

Tumour necrosis factor (TNF-α)

TNF-α is a pro-inflammatory cytokine that was first identified as a protein produced by lymphocytes and macrophages with the ability to induce apoptosis of tumour cells. It is produced mainly by macrophages in acute inflammatory responses to bacteria and other microorganisms.

Despite its tumour suppressor properties, TNF-α is directly related to the progression of several types of tumours, since its chronic production maintain a pro-inflammatory profile in the tumor microenvironment and increase the release of matrix metalloproteinases (MMPs), IL-6, among other pro-inflammatory factors.

In a murine model of osteosarcoma induced by the transfer of AX mesenchymal cells from INK4a-deficient to wild type mice, TNF-α produced locally by macrophages promoted tumour progression and growth by keeping osteosarcoma cells in an undifferentiated state via extracellular signal-regulated protein kinases (ERK). Treatment with the TNF-α inhibitor Etanercept® inhibited tumour growth, increased differentiation of osteoblasts and increased survival, highlighting the pro-tumourigenic effect of TNF-α in osteosarcoma. Furthermore, study suggests an association between TNF-α polymorphisms and a higher risk to the development of osteosarcoma.

Interleukin-2 (IL-2)

IL-2 is a factor of growth and activation of T and NK cells, which increases tumour immunogenicity. Although IL-2 is not required for the development of regulatory T cells (Tregs) - a subpopulation of T lymphocytes characterized by expression of CD25+ and the transcription factor forkhead box P3 (FOXP3) that have an important role in suppressing tumour-specific immunity - in the thymus, it is essential to the survival, physiological expansion and function of Tregs in the periphery.

IL-2 courses administered alternated with pre- and post-operative polichemotherapy in osteosarcoma treatment have been shown to increase the number and activity of NK cells, which correlated with the improved prognosis of patients. Likewise, patients with a lower activity of NK cells in the periphery have been shown to be more predisposed to developing cancer and to a poor prognosis.

New players in osteosarcoma

Interleukin-15 (IL-15)

IL-15 is another member of the family of interleukin-2. IL-15 was identified due to its capacity to stimulate the proliferation of IL-2-dependent CTLL-2 T-cell line in the presence of neutralising anti-IL-2 antibodies. Given that IL-2 and IL-15 share common signalling components (IL-2/15Rβγc), evidence to date suggests that the interaction of IL-15 with its receptor in various cell types leads to signalling events that are similar, or identical, to those elicited by IL-2. These include activation of the JAK/STAT signalling pathways. Because IL-2/15Rβ is associated with Jak1 and γ chain is associated with Jak3, IL-15 binding results in STAT3 and STAT5 phosphorylation, respectively.

IL-15 is considered a potential immunotherapeutic agent against tumours due to its important role in the development, proliferation and/or activation of CD8+ T lymphocytes and NK cells. Previous studies have shown that osteosarcoma cell lineages appear to be sensitive to the cytotoxic activity of NK cells activated by IL-15.
IL-17 is the signature cytokine of Th17 cells, but which can also be synthesised by other cell types, such as NK, CD8⁺ and γδ T cells [82, 83, 84]. Although its role in tumorigenesis is still controversial [85, 86], the presence of IL-17 has been verified and associated with poor prognosis in different types of cancers [87, 88].

A previous study has shown that, contrary to osteosarcoma cells that express low levels of the IL-17 receptor A (IL-17RA), those with high expression became more sensitive to the cytolytic activity of NK cells upon treatment with IL-17 [89]. In stromal cells and fibroblasts, IL-17 induces the production of a variety of angiogenic mediators, including VEGF [90]. In fact, IL-17RA expression correlated with VEGF production by osteosarcoma lineages [91].

In vivo, it has been shown that IL-17A/IL-17RA interaction promoted metastasis in nude mice (athymic animals that lack T cells) injected with osteosarcoma cell lineages high expression of IL-17RA and that were additionally transfected with IL-17 coding gene [92]. Results from clinical trials demonstrated that osteosarcoma patients who had metastasis presented the highest IL-17 serum levels [91]. Such body of evidence indicates the IL-17 prognostic role for osteosarcoma, pointing out this interleukin as a potential therapeutic target [91, 92].

**Interleukin-34 (IL-34)**

IL-34, which was recently discovered, is a cytokine that was characterised for its ability to form macrophage colonies in human bone marrow cultures. Its role has been compared to the cytokine macrophage colony-stimulating factor (M-CSF) [93] due to their synergic action in inflammation [94]. IL-34 gene is widely expressed in many tissues and organs [95], and its signalling also occurs upon binding to the M-CSF receptor (CSF-1 receptor), which is expressed in human mononuclear phagocytes [93].

Like M-CSF, IL-34 promotes the proliferation and survival of the myeloid lineage, and favors macrophage polarisation to the M2 immunosuppressive profile [14, 96, 97, 98]. In addition, IL-34 expression has been verified in several tumour types and has correlated with poor prognosis [95]. Particularly in osteosarcoma, IL-34 has been shown to increase tissue irrigation, as well as to recruit and polarise macrophages to the M2 profile, reinforcing its role as a pro-metastatic, angiogenic agent and as a promoter of tumour progression [98].

**CXCL12**

CXCL12 is an important chemokine for recruiting cells that express CXCR4 and CXCR7 receptors, which are associated with metastatic disease in several tumour types CXCL12 is produced by osteoblasts and osteosarcoma cell lineages [99] and is abundantly expressed in the lungs [100].

The influence of CXCL12 on osteosarcoma remains controversial. CXCR4 expression in the tumor microenvironment has been linked to poor prognosis because it facilitates tumour progression and lung metastasis [101, 102]. Conversely, a previous study that analysed tissue samples of 223 patients showed a positive correlation between CXCL12 and CXCR4 expression and the lower incidence of metastasis, with the consequent improvement of patient survival [103].

**CXCL8**

also known as IL-8, is a pro-inflammatory cytokine with an important role in the tumor microenvironment because its expression and/or of its receptors CXCR1 and CXCR2 are increased in endothelial cells and in tumour-associated cells such as macrophages (TAM) and neutrophils (TAN), as well as in tumour cell lineages and cancer cells of tissue biopsies [104]. Therefore, CXCL8 has been associated with the promotion of angiogenesis, chemotaxis and activation of neutrophils, as well as with proliferation, migration and invasion of tumour cells [104, 105].

CXCL8 polymorphisms have been associated with increased risk of osteosarcoma [106]. Osteosarcoma cell lineages that express high levels of IL-6 and CXCL8 respond in an autocrine manner to these cytokines, and develop lung metastases more rapidly than lineages with a low expression of IL-6 and CXCL8 [107]. Studies have shown that CXCL8 serum levels are significantly increased in osteosarcoma patients in comparison to healthy volunteers [21, 108]. Moreover, among osteosarcoma patients, those who had tumours larger than 8 cm presented higher CXCL8 serum levels compared to patients with smaller tumours, indicating its correlation with disease progression [21].

**Fractalkine (CX3CL1)**

FK exists in two forms: as a 95 Kda membrane-anchored protein or as a chemokine released following protease cleavage from the mucin stalk. After its release, FK can act as a potent chemoattractant for monocytes, NK cells and T lymphocytes [109, 110]. It can also tightly adhere to the chemoattracted cells through FK-CX3CR1 interaction in its

membrane-immobilised form. The FK receptor CX3CR1 is expressed mainly on NK cells, CD8+ T cells and CD14-monocytes, which are consistent with FK potent chemotactic activity for these cells [111, 112, 113].

Due to its potential to recruit cytotoxic T cells and NK to the tumor microenvironment, an important role has been ascribed for FK in osteosarcoma [114]. In a murine osteosarcoma model induced by the administration of K7M2 cells, animals treated with the non-viral vector of the CX3CL1 gene showed decreased pulmonary metastasis, pointing out to this chemokine as a potential immunotherapeutic approach [114].

Considering the above-mentioned information, an overview of the emerging main cytokine networks in osteosarcoma’s tumor microenvironment is depicted in the Figure 1.

**Immunotherapy in emerging cytokine networks**

Cancer immunotherapy has evolved since sarcoma control was observed in patients after erysipela infections [115]. It has been described that cytokine-mediated signalling affects development as well as behaviour of bone cells, which are related to osteosarcoma tumorigenesis [13]. Therefore, targeting signalling pathways in cytokine networks may have promising results in osteosarcoma treatment.

It has been previously shown that the slow infusion of high doses of rIL-2 in paediatric patients with osteosarcoma led to the complete remission of the disease in 50% of the patients tested, while the other half showed disease progression [116]. Significant toxicity was observed during the study, indicating that rIL-2 systemic administration in paediatric patients may not be feasible in the long term. In mice, intranasal administration of rIL-2 increased the survival rate of animals with metastatic osteosarcoma [117], indicating that IL-2 can be useful through restricted administration. However, more randomised controlled trials are needed to determine the effectiveness of this treatment.

Ex vivo studies have demonstrated that osteosarcoma cells of adult patients were susceptible to the cytolytic activity of IL-15-stimulated NK cells [118]. Clinical studies are being conducted to evaluate the potential of IL-15-stimulated NK cells to fight osteosarcoma in children with cancer [119].

IFN-α has shown to be effective in both in vitro and in vivo suppression of osteosarcoma cells in an animal model [120]. IFN-α presented apparent clinical efficacy when used daily as adjuvant therapy in the treatment of post-operative osteosarcoma, increasing patient’s survival [121]. Treatment of
osteoarcoma patients with interferon α-2b coupled to polyethylene glycol (IFN α-2b-PEG) - which enhances the half-life of IFN-α in the body, reducing the number of necessary administrations [122], as adjuvant therapy to standard MAP protocol (methotrexate®, doxorubicin® and cisplatin®) is in the clinical phase of testing [123]. However, such treatment has shown similar results to those of the standard MAP protocol with regards to toxicity, tolerance, and survival time [124]. IFN β has not shown promising results as an adjuvant therapy to chemotherapy [125]. In vitro studies have shown that IFN-γ-activated macrophages are able to inhibit the growth of osteosarcoma cells [126], although in vivo studies have not been conducted to confirm such a hypothesis.

In vitro treatment of osteosarcoma cells with a TGF-β1 kinase inhibitor induced apoptosis and increased the chemosensitivity of tumour cells [127]. To date, the effectiveness of TGF blockade for inhibiting osteosarcoma progression in vivo has not been evaluated.

In adult patients with osteosarcoma, the induction of non-specific cytokines by Liposomal-Muramyl Tripeptide Phosphatidyl-ethanolamine (L-MTP) - a synthetic analogue of the muramyl dipeptide derivatives of the mycobacterial cell wall that can significantly stimulate the innate immune response [128] - increased the serum concentrations of IL-6, TNF-α and neopterin. While IL-6 and TNF-α are associated with poor prognosis in osteosarcoma, the addition of L-MTP to the standard chemotherapy treatment of children with osteosarcoma has helped to increase patient’s survival, although it has not affected the occurrence of metastases [129].

Conclusion

This review allowed us to gather and synthesize evidence on the functions of classic cytokines as well as on the recent protagonists in the emerging cytokine networks in osteosarcoma. Furthermore, it was possible to outline a panorama of therapeutic targets that encompass the complexity of this network.

Emphasis has been recently placed on the understanding of the complex cytokine networks in an attempt to improve osteosarcoma immunotherapy. However, there are still several gaps in the scientific literature to be addressed, given the clinical heterogeneity and the variable and individual immune response of the host.

Conflicting interests

The authors have declared that no conflict of interests exist.

Abbreviations

RB1: retinoblastoma; p53: tumor protein 53; HIC1: hypermethylated in cancer 1; SNP: single nucleotide polymorphisms; GRM4: glutamate receptor metabotropic 4; cAMP: cyclic adenosine monophosphate; IL-6: interleukin-6; IL-6R: interleukin-6 receptor; gp130: glycoprotein 130; JAK: janus kinase; STAT: signal transducer and activator of transcription; siRNA: silencing RNA; VEGF: vascular endothelial growth factor; ASK1: apoptosis signal-regulating kinase 1; p38: mitogen-activated protein kinases; AP-1: activator protein 1; JAK-: janus kinase; ICAM-1: intercellular adhesion molecule-1; RTKs: receptor tyrosine kinases; PIGF: placental growth factor; VEGFR: vascular endothelial growth factor receptor 1; NRPs: neuropilins; PI3K: phosphatidylinositol-3,5-bisphosphate 3-kinase; AKT: protein kinase B; TGFβ: transforming growth factor beta; TGFβ R-: transforming growth factor beta receptor SMAD: intracellular proteins; EMT: epithelial-mesenchymal transition; IFN: interferon; IFNAR-: interferon alpha/beta receptor; IFNGR-: interferon gamma receptor; IFN-λ-: interferon lambda; IL-29: interleukin-29; IL-28: interleukin-28; IFNλ-R: interferon lambda receptor; IL-10R2: interleukin-10 receptor; NK: natural killer; TNF: tumour necrosis factor; MMPs: matrix metalloproteinases; AX: accelerated bone formation; c-MYC: v-myc avian myelocytomatosis viral oncogene homolog; ERK: extracellular signal-regulated protein kinases; IL-2: interleukin-2; Tregs: regulatory T cells; FOXP3: forkhead box P3; IL-15: interleukin-15; IL-2/15Rβγc: interleukin-2/15 receptor beta-gamma chain; IL-2/15Rβ: interleukin-2/15 receptor beta; IL-17: interleukin-17; IL-17RA: interleukin 17 receptor A; IL-34: interleukin-34; M-CSF: macrophage colony-stimulating factor; CSF-1: colony stimulating factor 1; CXCL12: stromal cell-derived factor-1; CXCR4: chemokine receptor type 4; CXCR7: chemokine receptor type 7; CXCL8: chemokine (C-X-C motif) ligand 1; CXCR1: chemokine (C-X-C motif) receptor 1; CXCR2: chemokine (C-X-C motif) receptor 2; TAM: tumour- and macrophages; TAN: tumor-associated neutrophils; CX3CL1: chemokine (C-X-C motif) ligand 1; FK: fractalkine; PEG: polyethylene glycol; L-MTP: Liposomal-Muramyl Tripeptide Phosphatidyl-ethanolamine.

Author contributions

LCLJ and GPS have designed the study. LCLJ; DSCS; AV; JCS; LCV; AF; MFS; RAGL and GPS have done the data analysis, manuscript writing as well as final approval of the manuscript.

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