Clinics of Surgery

Review Article

ISSN: 2638-1451 | Volume 7

The Role of IL-35 and IL-37 in Prostate Cancer

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Received: 26 May 2022
Accepted: 07 Jun 2022
Published: 13 Jun 2022
J Short Name: COS

Keywords:

IL-35, IL-37; Prostate cancer; Tumour associate macrophages

Citation:

Bao S. The role of IL-35 and IL-37 in prostate cancer. Clin Surg. 2022; 7(12): 1-6

1. Abstract

Prostate cancer is still a major challenge, due to its unacceptably high mortality and morbidity in a small proportion of patients. The development of prostate cancer is closely related to local infection and/or inflammation, which is associated with dysregulated host immunity. IL-35 and IL-37, anti-inflammatory cytokines, play an important role in the maintenance of homeostasis. Dysregulated IL-35 and 37 have been detected in many autoimmune diseases. In prostate cancer patients, local and systemic expression of IL-35 is correlated with Gleason score, differentiation, invasion, as well as prognosis. IL-37 boosts radiosensitivity in prostate cancer, inhibits proliferation and induces apoptosis of prostate cancer cells. IL-35 and IL-37 enhance macrophages to polarise towards M2 form of tumour associate macrophages in the tumour micro-environment to promote tumorigenesis. However, there is no simple answer for the particular role(s) of IL-35 and IL-37 during the development of prostate cancer, which may be related to the complex nature of host immunity, consisting of leucocytes and professional antigen presentation cells. Whilst IL-35 and IL-37 promote the development of prostate cancer, the precise underlying mechanism remains to be explored. The finding provides some insight in the potential role of precision medicine in exploring targeted therapy, with the potential to boost more specific cancer killing while reducing adverse effects.

2. The role of IL-35 and IL-37 in prostate cancer

2.1. Therapeutic potential Prostate cancer

Prostate cancer is closely related to local infection and/or inflammation [1], often starting from benign prostate hyperplasia and gradually developing into malignancy. The average age of prostate cancer patients varies for different regions/countries, and is perhaps related to genetic background [2]. Prostate cancer continues to attract great attention from both clinicians and basic scientists due to its rather high mortality and morbidity, particularly amongst a small sub-set of patients who develop advanced disease, e.g., metastatic castration-resistant prostate cancer (mCRPC) [2], although the incidence is gradually decreasing. It is important to note that prostate cancer is a treatable malignancy if it is detected at an early stage, allowing proper management with desirable outcomes. The treatment of prostate cancer includes surgery, chemotherapy, hormonal manipulation and radiotherapy [3, 4], and the most recent anti PD-1/PD-L1 immune checkpoint therapy [5]. However, some prostate cancer patients at the advanced stage can develop resistance to therapy and may die of mCRPC [6], which compromises the outcomes of the management.

2.2. Carcinogenesis of prostate cancer

The carcinogenesis of prostate cancer is closely related to infectious and dietary agents, in addition to genetic factors [1], which is supported by data that show the incidence of prostate cancer is significantly reduced in cohorts that regularly use anti-inflammatory and anti-oxidative drugs [7]. Furthermore, the tumour micro-environment plays a critical role in the development of prostate cancer [8], in line with findings that highly produced proinflammatory cytokines are detected in prostate cancer, including TNF, IL-1β, IL-7, MIP-1[9], which are linked with poor prognosis. However, local inflammation has also been shown to have some anti-prostate cancer effects, e.g. direct injection of IFN-α has been used to inhibit prostate cancer with a promising outcome [10] and IL-12 is

able to inhibit cancer proliferation *via* regulating Th1 cells [11]. In contrast, anti-inflammatory cytokines, e.g. IL-10, inhibit prostate cancer proliferation *via* MMP-2/9 *in vitro* [12], as well as being closely related to an IL-10 polymorphism [13]. These observations have led to the question "do pro- or anti-inflammatory cytokines aid the development of prostate cancer?". There is no simple answer for this question, as many variables are involved, including the stimulation period, local environment, and stimuli. In order to maintain homeostasis in the microenvironment, host immunity plays a critical role to balance pro- and anti-inflammatory responses. It has been documented that the impact of cytokines during the development of prostate cancer has been termed a double-edged sword due to their simultaneous pro- and anti-cancer function [14]. More recently, reports are emerging of successful outcomes within a select group of metastatic castrate-resistant prostate cancer patients when anti-PD-1 and PD-L1 were applied, supporting the occurrence of dysregulated immunity against prostate cancer [5].

2.3. IL-35

IL-35 belongs to the IL-12 family, which includes IL-12, IL-23, IL-27 and IL-35 [15]. IL-35 consists of two subunits, i.e. Epstein-Barr-virus-induced gene 3 (Ebi3, which encodes IL-27b) and IL-12α (IL12a, which encodes IL-12a/p35). It has been reported that IL-35 is expressed in Foxp3 (forkhead box P3) Treg cells [16], macrophages [17], dendritic cells and tumour cells [18]. IL-35 plays an important role in the suppression of effector immune responses [19] for regulating/maintaining the homeostasis of the host immune response [20]. IL-35 acts as both paracrine and autocrine factors *via* converting effector T cells into IL-35-producing T cells, which further enhances the proliferation of Treg cells [21]. Interestingly, IL-35 can also be produced by $CD8^+$ Treg cells, thus inhibiting antigen presentation against prostate cancer. Any disturbance of IL-35 may cause serious complications, resulting in autoimmunity including rheumatoid arthritis [22], SLE [23], atherosclerosis [24], and inflammatory bowel disease [25]. However, upregulated IL-35 resulting in or resulting from the abnormal immunity in the focal lesions is debatable, perhaps acting at both a paracrine and autocrine level.

2.4. IL-37

IL-37 belongs to the IL-1 superfamily [26] [27], and is a 17–26 kDa protein that corresponds with a gene size of 3.617 kb [28]. IL-37 is detected in many leucocytes, epithelial cells and tissues including lymph nodes, arteries, lung, intestine and uterus [29, 30]. Because IL-37 is able to inhibit both innate [27] and adaptive immunity [31], IL-37 is considered to be an anti-inflammatory cytokine. Thus, IL-37 regulates/supresses the host immune response [32], and may also be involved in tumorigenesis [33]. The anti-inflammatory function of IL-37 [32] is partially due to the capacity to inhibit the maturation of dendritic cells [34], and/or to regulate polarisation of macrophages, i.e. promoting M2 but inhibiting M1 macrophages [35] (including tumour associate macrophages, which will be discussed in the next section). Abnormally expressed IL-37 has been observed in a number of auto-immune diseases, such as rheumatoid arthritis [36], psoriasis, Grave's disease and systemic lupus erythematous and inflammatory bowel disease [25], and gestational diabetes mellitus [37]. The anti-inflammatory role of IL-37 is perhaps *via* its capacity to compete with the function of pro-inflammatory cytokines [25, 36, 38]. We have recently reviewed how IL-37 effectively reduces the development of atherosclerosis [39], confirmed in an IL-37 transgenic animal model [40], and IL-37 provides protection during the development of colorectal cancer [41].

2.5. Tumour associate macrophages (TAMs)

Chronic inflammation is a critical contributing factor in carcinogenesis, particularly *via* intensive interactions among different infiltrating leucocytes and target cells [42]. There is often substantial recruitment of leucocytes [43], including macrophages within malignant tissues, accompanied by the secretion of cytokines and neovascularization within the tumour microenvironment [44]. The large number of infiltrating macrophages within the tumour microenvironment are termed tumour associated macrophages (TAMs) [45]. It has been reported that TAMs stimulate tumour invasion and migration, as well as augment angiogenesis of microvascular and lymphatic vessels [46] *via* improving immunosuppression [47]. Interestingly, it has also been observed that TAMs are capable of inhibiting cancer growth and metastasis [48]. The distinctive dual roles of TAMs in the micro-environment are perhaps linked to the different micro-environments within the different organs, resulting in differential polarization of macrophages from naïve M0 macrophages into classical activated M1 macrophages and alternatively activated M2 macrophages [49, 50]. The differential polarization of macrophages is closely related to the different microenvironments in the organs of different diseases [51-53] to produce pro- vs anti-inflammatory cytokines. M1 macrophages, expressing CD86 and CD40, are activated with classical stimuli, e.g. LPS+IFN-γ, which exclusively activate chemotaxis and recruitment of leucocytes function. M1 TAMs contribute to anti-tumour functions, including directly mediated cytotoxicity *via* releasing ROS and NO, as well as antibody-dependent cell-mediated cytotoxicity (ADCC) to kill tumour cells. On the other hand, M2 TAMs promote the occurrence and metastasis of tumour cells, *via* inhibiting the T cell-mediated anti-tumour immune response and promoting tumour angiogenesis, which leads to tumour progression [50]. More recently, the induction of M1 or M2 cells *in vivo* and *in vitro* has been described, yet functions of these two subsets remain to be clarified [54].

We have therefore reviewed the role of IL-35 and IL-37 in the development of prostate cancer in this mini-review.

2.6. The role of IL-35 in prostate cancer

There is a constitutive level of IL-35 expression within the normal prostate, determined by immunohistochemistry [55]. IL-35

expression is upregulated in benign prostate hyperplasia (BPH), and more significantly in prostate cancer tissues. IL-35 expression within prostate tissues is consistent with circulating IL-35 production within each cohort, with a gradual increase in the order from normal, BPH and prostate cancer, respectively [55]. Importantly, IL-35 expression in prostate cancer is associated with the Gleason scores, i.e. high IL-35 correlates with high Gleason score (poor differentiation) [55, 56], suggesting that IL-35 may be enhancing the development of prostate cancer. However, the source of IL-35 producing cells in prostate cancer has not been clearly identified. Based on recent immune histochemical data [55], IL-35 appears to be produced by the prostate cancer cells directly, rather than stroma. This is supported by other studies, reporting that breast cancer cells can produce IL-35 [18], and Treg-derived IL-35 inhibits anti-tumour T cell responses in lung cancer [19]. Such observation may explain the inverse correlation between expression of IL-35 and the differentiation of prostate cancer, suggesting that IL-35 promotes the development of prostate cancer. Interestingly, there is no significant difference of IL-35 expression in prostate cancers between older and younger prostate cancer patients in the report from Zhou's group [57], which is possibly due to two factors: the cut off is at 65 years, while the overall average age of the prostate cancer patients was close to 60. Thus, it is unlikely that there is much difference in the release of male hormone between these two aged groups; in addition, it is a single centre study with a limited number of patients, which may compromise the statistical power [55]. Interestingly, a close association between the expression IL-35 and prostate specific antigen (PSA) was also observed, which has been used as a reliable biomarker for prostate cancer [58]. The close linkage between IL-35 and PSA also strongly supports the idea that IL-35 enhances the development of prostate cancer [55]. Additionally, the observation that there are gradually increased circulating IL-35 levels in the three cohorts, healthy controls, benign prostate hyperplasia to prostate cancer patients, further supports the hypothesis that IL-35 is involved in the development of prostate cancer. Moreover, the level of circulating IL-35 positively correlates with prostate cancer differentiation, invasion and 5 year survival [55], which provides clear evidence to support the involvement of IL-35 in the carcinogenesis of prostate cancer. Thus, it has been suggested that IL-35 seems to be a reliable prediction marker for diagnosis of prostate cancer [57]. At a cellular level, Zhu, et al. has demonstrated that IL-35 promotes proliferation and invasion of prostate cancer *in vitro* [59], which is further supported by the finding in a prostate cancer animal model, showing that anti-IL-35 antibody treatment extends survival time in the animal model *in vivo*, perhaps *via* suppressing Treg cells [59].

The precise underlying mechanism of action of IL-35 during the development of prostate cancer is not fully understood. However, based on the known roles of IL-35 as an anti-inflammatory agent or in suppressing host immunity, it has been suggested that IL-35 does indeed promote prostate cancer local invasion and distance metastasis. There is no direct linkage between IL-35 and differentiation of macrophages, however, IL-35 enhances and boosts M2 macrophage polarization via IL-10, thus indirectly promoting cancer development. This hypothesis is supported by the recent observation that TAM numbers inversely correlate with the therapeutic effect of androgen deprivation therapies in prostate cancer. Additionally, TAMs are significantly correlated with circulating prostate-specific antigen, high GS (poor differentiation), and metastasis of prostate cancer [60]. Multivariate analysis demonstrates that infiltrating TAMs is a good predictor in poor prognosis of prostate cancer [60]. However, it remains to be clarified whether such infiltrating TAMs are M1 or M2, but it is believed that these are mainly M2 TAMs. This hypothesis is supported by the finding that the predominant TAMs are M2 macrophages in prostate cancer [61], and may act in both autocrine and paracrine fashions. Importantly, the increased number of M2 TAMs correlates with prostate cancer Gleason score and depth of invasion, but is inversely correlated with differentiation, which is also in line with the suggestion from others that M2 TAMs are pro-tumour, but M1 cells are anti-cancer [61]. Interestingly, the proportion of M1 vs M2 cell infiltrates in prostate cancer tissue does not appear to vary with age. This may be due to the fact that the majority of prostate cancer patients are rather old (68.9 ± 9.1 years). An additional factor is possibly related to the earlier detection and/or prevention of prostate cancer development. Thus, male hormone(s) appear to play no significant role within this aged cohort of prostate cancer patients. Interestingly, the M1 and M2 proportion is consistent in both pre-operative biopsy and post-operative histopathology [61], suggesting that the risk factor(s) for the development of prostate cancer, including the polarisation of macrophages, changes following removal of the primary prostate cancer. These findings suggest that M1 and M2 polarisations are determined *via* a paracrine fashion, i.e. not affected by the presence or absence of the primary prostate cancer. Of course, IL-35 certainly boost M2 terminal differentiation [62], which enhances angiogenesis, cancer development and metastasis [45]. Notably, the source of IL-35 within the tissues of prostate cancer may not only be derive from the tumour cells, a question that should be clarified in future studies.

Thus, it is reasonable to speculate that IL-35 promotes naïve M0 macrophages to differentiate into M2 macrophages, and subsequently promotes the development of prostate cancer *via* inhibiting effector cytotoxic T cells. These correlations need to be clarified in future studies.

2.7. IL-37 in prostate cancer

After an extensive literature search, no reports concerning the relationship between IL-37 and prostate cancer *in vivo* have been found. Additionally, no data are available concerning the constitutive expression of IL-37 within prostate tissue.

Radiotherapy is one of the more effective approaches in the treatment of prostate cancer, however, there is also side-effects in the irradiated region. Ideally, it would be beneficial to treat prostate cancer patients with a low dose of radiation, however, some prostate cancer patients develop locally persistent/recurrent tumours [63]. One approach is to prime the patients with different cytokines to improve radiosensitivity [63]. More recently, Ding *et al* demonstrate that there is no obvious change of prostate cancer cell proliferation or apoptosis in the presence of exogenous IL-37 *in vitro* [64]. However, IL-37 enhances the radiation sensitivity of the prostate cancer, showing that substantial inhibited cellular proliferation following co-treatment of IL-37 and radiation, *via* enhanced apoptosis, even with a minor dosage of radiation. Such data suggest that IL-37-primed cancer cells exhibit increased sensitivity toward radiation, i.e. effectively reducing the dosage of radiation to minimise side-effects. Furthermore, exploration of the mechanistic role of such co-treatment revealed the possible pathways for inhibiting prostate cancer proliferation were *via* increasing p27, p53, and PCNA (an anti-proliferative molecule), as well as enhancing apoptosis *via* Fas and Bax (two pro-apoptotic molecules) [64]. Such data suggest that IL-37 is beneficial for the management of prostate cancer. This is in line with the finding that IL-37 supresses proliferation of cervical cancer directly *in vitro* [65] *via* the STATS3 pathway. In addition, it has been reported that IL-37 inhibits the development of lung carcinoma *via* downregulating angiogenesis using the Wnt5a/5b pathway [66]. Although there are significant differences in the microenvironments among prostate, cervical and lung cancers, the findings from these studies indeed support the protective role of IL-37 during the development of cancer, which may occur *via* different sensitivities and/or be regulated differently by the host immunity *via* differential regulations of IL-37 within these microenvironments. The precise underlying mechanism of IL-37 action during the development of prostate cancer remains to be explored in the future.

Moreover, there is a close relationship between IL-37 and the development of macrophages. As described above, M1 macrophages function in an anti-cancer manner, however, M2 macrophages act in a pro-cancer fashion. Zhou, *et al*. demonstrate that IL-37 also inhibits M1 polarization, while enhancing M2 macrophage polarization *via* Notch1 and the classical NFKB pathways [67] in human aortic plaques and *in vitro*. It has been reported that IL-37 inhibits pro-inflammatory mediators to reduce the development of prostate cancer [1]. The observation that IL-37 inhibits M1 but promotes M2 macrophage polarization *in vitro* [67] suggests that IL-37 is likely to enhance the development of prostate cancer. Recombinant human IL-37 attenuates inducible nitric oxide synthase production. M2 macrophages are able to promote an anti-inflammatory microenvironment, while contributing towards the development of prostate cancer. Thus, it is logical to speculate that IL-37 enhances the development of prostate cancer, however, this hypothesis may superficially seem to contradict the findings above that IL-37 has the capacity to boost radiosensitivity when treating prostate cancer.

The question raised here is ‘does the role of IL-37 contribute to the development of prostate cancer, i.e. is IL-37 anti- or pro-carcinogenic?’. Such a discrepancy invites speculation that IL-37 may have dual roles during the development of prostate cancer, which may be related to stage and/or other risk factors or IL-37 may promote cancer growth, it seems likely that this also makes the cancer cells more radiosensitive, so on balance there may be a positive therapeutic effect to IL-37/radiotherapy dual effects There is no simple answer for this particular question, which may be related to the orchestration of the host immune response, which *in vivo* consists of the whole population of leucocytes. To answer these questions, further investigation should be performed in depth to investigate IL-37 expression, macrophage infiltration and polarization, correlated with the degree of prostate cancer invasion/development, and the prognosis of prostate cancer patients’ samples, as well as, in animal models of IL-37 manipulated mice.

In conclusion, IL-35 and IL-37 appear to contribute to the development of prostate cancer, perhaps primarily *via* promoting M2 TAM polarization, however, the precise underlying mechanism remains to be explored. Such data provide insight into the potential of exploring targeted therapies, by increasing more specific cancer killing while reducing adverse effects.

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