Cytokine 118 (2019) 42–47

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Review article

Tumor inherent interferons: Impact on immune reactivity and immunotherapy

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ARTICLE INFO

Keywords:
Interferon
Cancer
Immunotherapy
Tumor infiltrating lymphocytes
Tumor microenvironment

ABSTRACT

Immunotherapy has revolutionized cancer treatment, with sustained responses to immune checkpoint inhibitors reported in a number of malignancies. Such therapeutics are now being trialed in aggressive or advanced cancers that are heavily reliant on untargeted therapies, such as triple negative breast cancer. However, responses have been underwhelming to date and are very difficult to predict, leading to an inability to accurately weigh up the benefit-to-risk ratio for their implementation. The tumor immune microenvironment has been closely linked to immunotherapeutic response, with superior responses observed in patients with T cell-inflamed or 'hot' tumors. One class of cytokines, the type I interferons, are a major dictator of tumor immune infiltration and activation. Tumor cell inherent interferon signaling dramatically influences the immune microenvironment and the expression of immune checkpoint proteins, hence regulators and targets of this pathway are candidate biomarkers of immunotherapeutic response. In support of a link between IFN signaling and immunotherapeutic response, the combination of type I interferon inducers with checkpoint immunotherapy has recently been demonstrated critical for a sustained anti-tumor response in aggressive breast cancer models. Here we review evidence that links type I interferons with a hot tumor immune microenvironment, response to checkpoint inhibitors and reduced risk of metastasis that supports their use as biomarkers and therapeutics in oncology.

1. Introduction

Cancer immunology is the most rapidly expanding field in cancer research, with the importance of immunity in cancer pathogenesis now well accepted in solid malignancies. The composition of the tumor microenvironment (TME) is a major dictator of disease progression, with the presence of tumor infiltrating lymphocytes (TILs) a positive prognostic indicator in a number of cancers, including triple negative breast cancer (TNBC) and melanoma [1,2]. The discovery that the anti-tumor immune response is closely linked to patient outcome has initiated the era of cancer immunotherapy, where dramatic responses to some agents have been observed in cancers that were considered incurable, such as metastatic melanoma. One of the most common classes of immunotherapeutics receiving attention in oncology are the checkpoint inhibitors. Aimed at releasing the breaks on the immune system, these agents essentially block the interaction of tumor or stromal cell-derived checkpoint ligands with interacting receptors on T cells. One of the most researched and targeted is the interaction between programmed death ligand 1 (PD-L1) and its receptor PD-1, that functions to prevent overstimulation of the immune system by deactivating T cells [3,4]. The discovery that tumor cells exploit this axis via cell surface expression of PD-L1 [5,6] has led to the development of PD-L1 and PD1-targeted therapeutics. Antibodies targeting PD-1 (Nivolumab and pembroluzimab) have transformed the care of advanced melanoma with 3-year patient survival rates of over 50%, a drastic improvement over chemotherapy alone [7–9]. The success of such agents in melanoma has been somewhat attributed to the high UV-induced mutational load producing neoantigens, and the extensive T cell infiltrate primed for activation post checkpoint inhibition. However, durable clinical responses do not occur in all patients despite a high mutational load and lack of response is associated with immune cell poor or 'cold' tumors [10]. Although breast cancer has a much lower mutational frequency, trials using such checkpoint inhibitors have begun yet the few reports to date have been underwhelming. Clinical trials using pembroluzimab in patients with advanced triple negative breast cancer (TNBC), the highest PD-L1 expressing subtype, have reported an overall response rate of 18%, with a complete response reported in only 1 patient [11]. In this study, tumor expression of PD-L1 was not a sufficient marker of response. In fact, the expression of stromal PD-L1 in TNBC predicts a good prognosis in the absence of immunotherapy [12,13]. This indicates that apart from measurement of PD-L1, prediction of responders relies on evaluation of the nature of TILs and the

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https://doi.org/10.1016/j.cyto.2018.04.006
Received 11 February 2018; Received in revised form 5 April 2018; Accepted 6 April 2018
Available online 19 April 2018
1043-4666/

profile of immunoactivating cytokines, such as the type I and II IFNs-both of which induce checkpoint inhibitor expression [14–16]. This review discusses the impact of IFN signaling on the TME, and the evidence that tumor inherent IFN signals are candidate biomarkers of patient prognosis and response to both conventional and immunotherapeutics.

2. The tumor microenvironment

Tumor cells do not exist as a single entity but rather as a complex network with non-neoplastic cells that form the TME and dictate tumor behavior and progression. The TME includes the extracellular matrix (ECM), fibroblasts, cells that comprise the blood vessels including endothelial cells (ECs) and, most relevant to this review, a range of immune cells [17]. Cells present in the TME can form a supportive niche that promotes tumor persistence, proliferation and progression through the provision of growth factors, cytokines, nutrients and oxygen [18,19]. Often referred to as a wound that won't heal, tumors can secrete cytokines that encourage the migration of immune suppressive cells into the microenvironment, growth of new blood vessels and rearrangement of the ECM, forming a pro-inflammatory niche, optimal for tumor survival [18–20]. Conversely, the TME can be one which fosters tumor elimination and/or control through the accumulation of cytotoxic immune cells and anti-tumorigenic cytokines [17,21]. The accumulation of TILs has proven to provide valuable insight into how a tumor is expected to behave in response to therapies and whether a patient is likely to have a favorable outcome. This has contributed to a paradigm shift whereby the focus of conventional therapeutics is not solely on direct cytotoxic effects but also on increasing tumor cell immunogenicity to promote immune-mediated cell death. This has also contributed to the wave of new immunotherapeutic approaches aimed at promoting an immune active microenvironment whilst increasing the visibility of tumor cells, tipping the balance towards a 'hot' tumor that fosters immune-mediated tumor elimination.

3. Defining hot and cold tumors

The immunogenicity or heat of a tumor depends on its antigenicity and several other immunomodulatory factors that are produced either by tumor or host cells in the TME [22]. High TILs are well documented in cancers with a high mutational load, yet a correlation between immune infiltrate and a favorable prognosis has also been reported in other solid malignancies, such as breast and prostate cancer [2,23–25]. Although commonly used as a measure of a hot tumor, a TIL score alone does not allow an assessment of the immune active state and the balance between immune effector and suppressor cells that are likely to have opposing effects on tumor progression. Whilst moving into the era of immunotherapy, characterization of TILs and their ability to promote or suppress the anti-tumor immune response should be considered to give us a more robust understanding of the immunoreactivity of an individual tumor to predict its fate.

The measurement of T lymphocytes has added to our knowledge of the immune status of a tumor. Characterization of TILs in melanoma had led to the emergence of the 'T cell-inflamed' tumor that predicts a favorable prognosis and immunotherapeutic response [26–28]. Initially characterized by analysis of the tumor transcriptome, T cell-inflamed tumors have enhanced T cell transcripts, chemokines associated with T cell recruitment and a type I IFN signature [28] and an associated increase in infiltrating $CD8^+$ T cells, along with B cells and macrophages [28]. In these tumors, an increase in immune suppressive proteins is also evident including FoxP3, indoleamine-2.3 dioxygenase and PD-L1, raising the possibility that T-cell inflamed tumors have inherent immune escape mechanisms, contributing to their increased response to immunotherapies targeting these proteins [29]. The 'non T cell-inflamed' tumor is immune cell low and lacks a T cell infiltrate and also the expression of the above mentioned immune suppressive transcripts [28,30]. Based on these characteristics, a non T cell-inflamed tumor is unlikely to respond to checkpoint inhibitors [30]. The link between the $CD8^+$ T cell infiltrate and a favorable outcome has been reported in other cancers including breast, colorectal and non-small cell lung cancer, as has the correlation between a T cell infiltrate and PD-L1 expression [13,31–35]. The value of further characterization of $CD8^+$ T cells has been revealed in NSCLC where infiltration of $CD8^+$/$CD45RO^+$ cells, indicative of memory T cells, was linked to favorable outcome [35]. Furthermore the accumulation of $CD8^+$ T cells and in particular, PD-1 expressing $CD8^+$ T cells, in the TME is an indicator of response to anti-PD-1 therapy [36–38]. Together, this supports measurement of $CD8^+$ T cells as an important component in predicting a hot TME as well as response to immunotherapy.

Further to the T cell inflamed tumor, there are other cells capable of inducing a robust anti-tumor immune response. With the ability to kill tumor cells without prior sensitization, natural killer (NK) cells play a large role in controlling the initial outgrowth and spread of a tumor [39–41] and are a major source of IFNγ in the TME which is cytotoxic to tumor cells and crucial in the priming and differentiation of some T cell subsets [42–44]. Whilst less explored than T cells, extensive tumor infiltrating NK cells are associated with prolonged disease-free and overall survival (OS) in colorectal carcinoma (CRC), gastric cancer and prostate cancer [45–47].

Analysis of TIL score alone overlooks another class of tumors, heavily infiltrated by immune suppressive cells and those that promote growth and invasion (Fig. 1). Immune cells that accumulate in the TME and support tumor growth and immune suppression include regulatory T cells (T_{regs}), myeloid derived suppressor cells (MDSCs), and macrophages. T_{regs}, classified as CD4+ CD25+ FoxP3+ T cells, suppress the induction and proliferation of effector T cells and secrete pro-tumorigenic cytokines [48]. Although a FoxP3 signature is expressed in a T cell-inflamed tumor that is associated with a good prognosis as discussed for melanoma, many studies have highlighted that the ratio between $CD8^+$ T cells and $CD4^+FoxP3^+$ cells is imperative in determining their prognostic impact. A high $CD8^+$ T cells to $CD4^+FoxP3^+$ cell ratio is associated with prolonged relapse free survival (RFS) and OS in CRC, ovarian cancer and breast cancer [49,50] [51]. Although most thoroughly studied in mouse models of cancer, polymorphonuclear (PMN-MDSCs, $CD11b^+$ $Ly6G^+Ly6C^{lo}$) and monocytic (M-MDSCs, $CD11b^+Ly6G^-Ly6C^+$) MDSCs [52,53] function to suppress T cell responses via production of reactive oxygen species or nitric oxide and the promotion of T_{reg} development [52,54–57]. MDSC accumulation has also been linked to tumor progression and a shortened survival in a number of cancers (reviewed in [58]). M-MDSCs can also differentiate into tumor associated macrophages (TAMs), promoting angiogenesis invasion and metastasis [19,59,60]. The presence of TAMs in the TME is another hallmark of the 'non-T cell inflamed' tumor, as is the accumulation of fibroblasts [30,61]. Macrophage characterization includes M1 'classical' or M2, 'alternative' populations, mirroring the Th1 and Th2 (T helper cells) nomenclature, with very different roles in disease progression and therapeutic resistance (reviewed in [62,63]). Tumor associated macrophages (TAMs) are typically M2 macrophages, that among other immune suppressive functions secrete proteases such as MMPs to promote tissue remodeling, angiogenesis and metastasis [59,64–67]. Accordingly, increased TAMs has been reported to be a poor prognostic indicator in breast, ovarian, gastric, bladder, oral and thyroid cancer [68]. Based on the functional and prognostic implications of Tregs, MDSCs and M2-like TAMs, research efforts are currently focused on their elimination or re-polarisation to promote or restore an immune-reactive TME.

Taken together, this highlights the need for further characterization of immune infiltrates and the tumor-induced cytokines that dictate the immune-reactive state. One key class of cytokines that have not only been implicated in TIL accumulation and promoting a T cell-inflamed tumor, but also in negative regulation of immune suppressor cells are the type I IFNs.

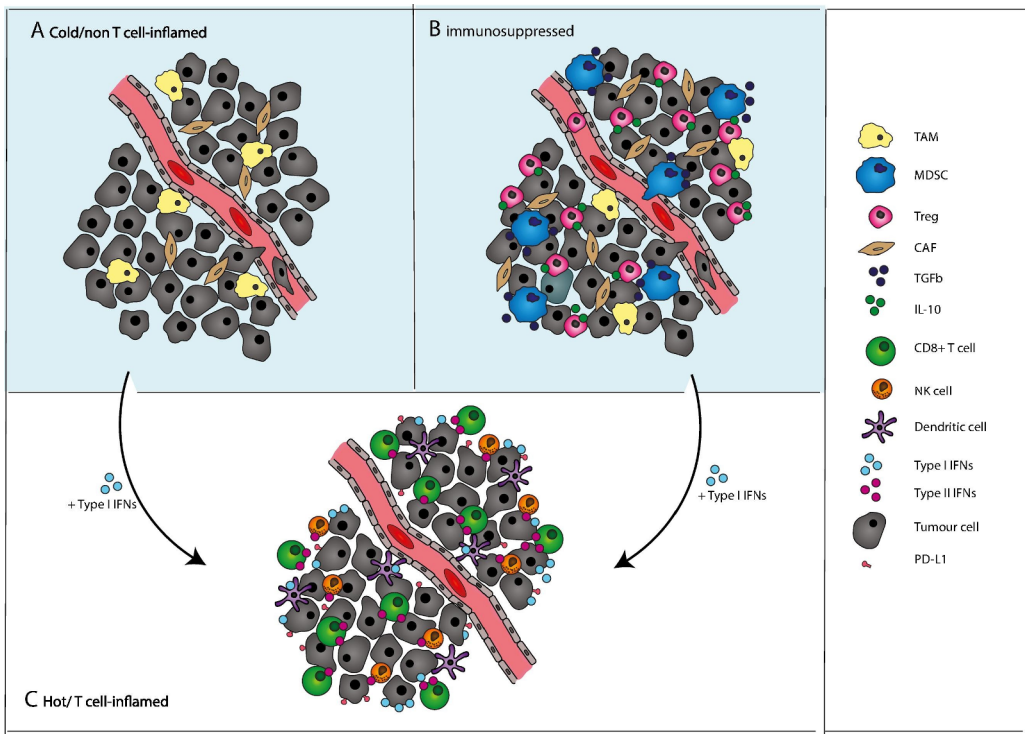

Fig. 1. Determining hot and cold tumors (A) The cold or non T-cell inflamed tumor has a lack of infiltrating immune cells including T-cells and a proportional increase in tumor associated macrophages (TAMs) and cancer associated fibroblasts (CAFs). (B) The immune suppressed tumor is heavily infiltrated by immunosuppressive cells; Tregs, MDSCs and TAMs along with CAFs and secretes immune suppressive cytokines, such as IL-10 and TGFβ. (C) The hot or T cell-inflamed tumor can be heavily infiltrated with dendritic cells (DCs) as well as T cells (cytotoxic) and natural killer (NK) cells capable of producing IFNγ. Tumor cell expression of type I IFNs, as well as IFNγ present in the TME leads to increased PD-L1 expression. Cold or immunosuppressed tumors (A, B) can be manipulated into becoming hot/T cell-inflamed tumors via the administration of type I IFN inducers, that increase IFN in the TME, promoting immune cell infiltration and activation, reducing the amount of immune suppressive cells and increasing the expression of PD-L1.

4. Type I Interferons and immunity

Type I IFNs are largely known for their role in the control and elimination of pathogens, being produced by a range of cells upon recognition of viral or bacterial components by pattern recognition receptors (PRRs) such as the toll-like receptors (TLRs) [69–71]. IFN signaling occurs via binding to the type I IFN receptors 1 and 2 (IFNAR1/IFNAR2) leading to Janus Kinase and signal transducer and activator of transcription (JAK-STAT) signaling that commonly promotes the formation of the IFN-stimulated gene factor 3 (ISGF3) [72]. Composed of STAT1, STAT2 and IRF9, ISGF3 binds to interferon-sensitive response elements (ISREs) inducing expression of interferon regulated genes (IRGs) [72]. There are thousands of IRGs that have been curated in the Interferome database [73] and lead to a multitude of responses including the induction of anti-proliferative, antiviral and immunomodulatory pathways. The expression of IRGs can regulate the activity of almost all immune cells, either through direct stimulation or indirectly through the induction of cytokines or chemokines, serving as a link between innate and adaptive immunity. NK cells, usually the first line of defense against both infection and cancer, are heavily reliant on type I IFNs for development, maturation and effector function, enhancing the cells ability to produce both IFNγ and IL-15 [74]. IFNs also promote DC differentiation, maturation and migration [75–77]. The process of T cell priming, which is mediated by DCs processing and presenting antigen, can be enhanced by type I IFNs [78]. A major source of type I IFNs in response to infection are a subset of DCs, plasmocytoid DCs (pDCs), promoting CTL priming via such production [79–81]. Further to enhancing antigen processing, type I IFNs can also directly increase MHC I expression, cementing their role as a key link between innate and adaptive immunity [82]. Additionally, direct impacts of type I IFNs on $CD8^+$ T cells include promoting survival and the secretion of IFNγ [83–85]. In addition to stimulating a plethora of immune effector responses, type I IFNs are also implicated in the negative regulation of immune suppressive cells, including T_{regs} and MDSCs [86–88], releasing the breaks on the immune response.

5. IFNs and the anti-tumor immune response

The link between type I IFNs and cancer control was first demonstrated over 50 years ago [89]. Initially seen to be important in the control of virally induced cancers, the administration of IFNα to tumor bearing mice was sufficient to control cancer growth, via inhibition of tumor cell proliferation [89]. Since then, studies have gone on to highlight the many roles that IFN can play in direct control of tumor cell growth via induction of tumor suppressor genes or inhibition of oncogenes (reviewed in [90]). In addition to direct cytotoxic and cytostatic effects, type I IFNs are also powerful inhibitors of angiogenesis, through reduction of pro-angiogenic factors and direct effects on EC proliferation, leading to tumor ischemic necrosis [91,92]. As mentioned previously, type I IFNs are imperative in the formation of an effective immune response so it is therefore no surprise that they are heavily implicated in anti-tumor immunity. Numerous studies have linked a loss of IFN signaling with accelerated tumorigenesis and an impaired anti-tumor response (reviewed in [93,94]). In a mouse sarcoma model the enhancement of tumor initiation and growth after loss of host IFNAR was linked to less efficient NK cell killing [74]. Our research using breast cancer models revealed similar findings, whereby loss of host IFNAR promoted metastasis to bone and decreased NK cell based immunity [95]. Other studies of cell-specific IFNAR loss have reported that $CD8\alpha^+$ DCs lacking IFNAR expression were deficient in antigen presentation and failed to control tumor growth [75]. Similarly tumor-induced suppression of IFNAR on CTLs in the TME leads to a loss of anti-tumor immunity and correlates with poor patient outcome in CRC [96]. In tumors derived from patients with aggressive TNBC, a decrease in intratumoral pDC IFNα production is associated with the increased accumulation of T_{regs} [97]. Additionally, IFNs can suppress T_{reg} proliferation [87] and the accumulation of MDSCs [88], both of which correlate with poor patient outcomes and direct suppression of cytotoxic lymphocytes [98–101].

6. Prognostic and therapeutic implications of tumor inherent IFNs

Recent studies suggest that tumor cell-intrinsic expression and secretion of IFNs is a key player in the anti-tumor immune cascade and

that the measurement of IFN signals and signatures could serve as prognostic biomarkers of relapse. Our studies utilizing metastatic breast cancer models revealed that tumor cells produce IFNs and that suppression of IFN signaling is a critical event in immune escape and the development of bone metastases [102]. In this study, interferon regulatory factor 7 (IRF7) and over 200 predicted IRF7 target genes were lost in bone metastatic tumor cells and interrogation of independent breast cancer cohorts revealed that primary tumor loss of this signature predicted an increased risk of bone metastatic relapse [102,103]. Restoration of this pathway through IFNα administration or IRF7 overexpression was sufficient to decrease bone metastasis in a TNBC mouse model [102]. In colorectal cancer (CRC), the capability of tumor cells to suppress IFNAR expression on CTLs was also associated with poor patient prognosis [96]. Furthermore, tumor cell downregulation of IFNAR in activated Braf melanoma led to a more aggressive phenotype [104]. Stabilization of IFNAR in these same melanomas was sufficient to restore IFN signaling, inducing senescence and halting melanoma progression [104].

Not only is tumor-inherent IFN important in immunogenicity and progression, it also influences therapeutic response. In breast cancer models, tumor response to anthracycline chemotherapeutics relies on intact tumor cell IFN signaling mediated by stimulation of TLR3 [105]. The reliance of tumor inherent IFN signaling on chemotherapeutic response was confirmed in breast cancer patients, where induction of a tumor inherent type I IFN signature after anthracycline treatment was associated with primary tumor response [105]. Importantly, other studies dissecting predictors of response to chemotherapy have found that induction of IRGs discriminates between chemo-sensitive and chemo-resistant tumors [106] and that low IRG expression correlates with poor response to chemotherapy in breast cancer [107].

Response to radiotherapy, like chemotherapy, has been demonstrated to be somewhat reliant on the induction of tumor immunogenicity. Radiotherapy can induce immunogenic cell death (ICD) in solid cancers leading to recruitment of immune cells through the release of chemokines [108]. After radiotherapy, the tumor becomes a source of tumor antigens, acting like an *in situ* vaccination due to the release of cellular contents [109]. Radiation induced cell death can impact surrounding cells ("bystander effect") via an increase MHC I, resulting in increases T cell recognition [108,110]. The accumulation of type I IFNs in the TME post radiation in a melanoma mouse model was imperative for tumor regression whereby mice lacking IFNAR did not respond to radiation therapy [111]. Research into dosing of radiation has now unveiled the advantages to more frequent, lower doses compared to larger single doses leading to an increased accumulation of cytosolic DNA and hence enhanced TLR stimulation and production of IFNβ and immune activation [112]. This supports a critical role of type I IFN signaling in response to radiotherapy.

7. Impact of IFNs on immune checkpoints

Immune cell activation is a tightly regulated process and as such IFN signaling not only induces suppressors of its own signaling pathway, such as the SOCS proteins [113], but also the expression of immune checkpoint proteins to prevent autoimmunity. The enhanced expression of PD-L1, post immune activation can be attributed to its regulation by interferon regulatory factors (IRF1, IRF9) and the JAK/STAT pathway which are induced upon both type I and II IFN signaling [16]. This may explain why the expression of PD-L1 has been associated with a favorable outcome in breast cancer [12,13], and that PD-L1 expression is associated with increased TILs and an IFN signature [12]. This has also been reported in metastatic melanoma [114], where immune checkpoint inhibitors are commonly used. As discussed earlier, PD-L1 and a type I IFN signature is associated with a T cell-inflamed tumor and thus a good prognosis, highlighting the need for effective type I IFN signaling in the elimination of tumors [28,29]. Based on this, studies were recently performed in models of TNBC to test the impact of systemic IFN-based therapies on PD-L1 expression, immune activation and response to immunotherapy [14]. In this study, the type I IFN inducer, poly (I:C), increased tumor cell PD-L1 expression and induced activation of circulating and tumor-infiltrating lymphocytes [14]. The administration of the TLR3 agonist improved metastasis-free survival yet this was further enhanced by the addition of anti-PD-1, which led to the induction of a tumor-specific immune response that was not induced using anti-PD1 alone [14]. This supports accumulating evidence that response to checkpoint inhibitors is linked to increased cell accumulation and activation in the TME [27,115]. Similar studies in other cancers have also implicated the use of IFN inducers, in the form of stimulator of interferon genes (STING) agonists, TLR agonists and viruses, in sensitizing cold tumors to anti-PD-1 therapy [10,116]. This work suggests that the presence of intact IFN signaling may be an indicator of those likely to benefit from checkpoint immunotherapy. Active IFN signaling is likely to enhance the expression of PD-L1 in host cells along with tumor cells, which is important considering that the expression of PD-L1 in immune cells, particularly antigen presenting cells, has been linked to response to anti-PD-1 based therapies in melanoma and ovarian cancer [117]. IFN inducers have promise in increasing patient response to checkpoint inhibitors, especially in patients with highly aggressive, immune-suppressed cancers. The impact of IFNs and their inducers on response to other emerging checkpoint inhibitors is yet to be determined. In cancers such as CRC, the impact of tumor-induced CTL IFNAR loss [96] on response to such interferon inducers needs to be tested.

8. Moving towards individualized immunotherapy

Recent work in breast cancer models has demonstrated that neoadjuvant immunotherapy is superior to treatment after tumor resection or upon detection of metastases [14,118]. These studies have revealed that the presence of tumors at the time of therapeutic administration is important in priming an effective anti-tumor response. The administration of therapy before tumor resection also allows for the analysis of biomarkers that predict response before and during treatment, providing a rationale for individualized immunotherapy [119]. Such an approach of sampling a tumor pre- and post-therapy has previously been utilized in bladder cancer and identified ICOS as a biomarker of response to checkpoint inhibitor, ipillumab, an anti CTLA4 antibody [120]. It is clear that tumor inherent type I IFNs are capable of promoting an immune reactive TME and have promise as prognostic biomarkers in oncology. Given that IFNs are heavily implicated in both immune cell regulation as well as PD-L1 expression, IFN-based biomarkers have great potential in predicting response to PD1/PD-L1 targeted therapies such as pembrolizumab and nivolumab. Importantly, IFN inducers such as TLR agonists are showing promise in increasing the heat on cold tumors, opening the door to new therapeutic opportunities for patients with aggressive immune cold tumors that could also benefit from checkpoint inhibitors.

Financial support

This work was supported by fellowship funding from the Victorian Cancer Agency (BSP).

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