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Dendritic cells, the T cell-inflamed tumor microenvironment and immunotherapy treatment response

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Abstract

The development of the most successful cancer immunotherapies in solid tumors, immune-checkpoint blockade, has focused on factors regulating T cell activation. Until recently, the field has maintained a predominately T-cell centric view of immunotherapy, leaving aside the impact of innate immunity and especially myeloid cells. Dendritic cells (DC) are dominant partners of T cells, necessary for initiation of adaptive immune responses. Emerging evidence supports a broader role for DCs in tumors including the maintenance and support of effector functions during T cell responses. This relationship is evidenced by the association of activated DCs with immune-checkpoint blockade responses and transcriptional analysis of responding tumors demonstrating the presence of type I interferon transcripts and DC relevant chemokines. T cell-inflamed tumors preferentially respond to immunotherapies compared to non-T cell inflamed tumors and this model suggests a potentially modifiable spectrum of tumor microenvironmental immunity. While host and commensal factors may limit the T cell-inflamed phenotype, tumor cell intrinsic factors are gaining prominence as therapeutic targets. For example, tumor WNT/β-catenin signaling inhibits production of chemokine gradients and blocking DC recruitment to tumors. Conversely, mechanisms of innate immune nucleic acid sensing, normally operative during pathogen response, may enhance DC accumulation and make tumors more susceptible to cancer immunotherapy. Elucidating mechanisms whereby DCs infiltrate and become activated within tumors may provide new opportunities for therapeutic intervention. Conceptually, this would facilitate conversion of non-T cell-inflamed to T cell-inflamed states or overcome secondary resistance mechanisms in T

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cell-inflamed tumors, expanding the proportion of patients who benefit from cancer immunotherapy.

Introduction

Antibodies directed against T cell surface co-inhibitory receptors such as Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) and the Programmed cell death protein 1 (PD-1) pathway can reinvigorate anti-tumor T cell responses. These treatments, collectively termed Immune Checkpoint Blockade (ICB), have become critical pillars in cancer treatment and demonstrate activity in a broad range of cancer types. However, the majority of patients receiving ICB do not have durable therapeutic responses. As clinical use of these antibodies has grown immensely, a key area of research aims to define patients likely to respond, or not, to checkpoint blockade. Key to this understanding are the principles of T cell activation in cancer, and in particular how immunotherapies shift the balance of tolerance towards anti-cancer immunity.

Although hypotheses have been advanced as to why some patient's tumors respond, or fail to respond, to checkpoint immunotherapy, most in the field have been in agreement that T cells, particularly $CD8^+$ cytotoxic T cells are the drivers of therapeutic response (1). Abundance of tumor infiltrating $CD8^+$ T cells, tumor mutational burden, and interferon- γ signatures are correlated with response to anti-PD-1 therapy (2–4). While biomarkers have become instrumental in understanding ICB, they do not explain the totality of treatment response and resistance. T cell presence alone in tumors may not be enough to induce anti-tumor immunity as numerous non-tumor specific T cells also infiltrate tumors (5). Therefore, this suggests an important need in the field to further understand and distinguish T cell-infiltrated from T cell-inflamed tumor microenvironments and further elucidate factors in the tumor environment driving antigen-specific T cell recruitment and activation.

Gene expression analysis of metastatic melanoma lesions identified a strong separation of samples based on T cell associated gene transcripts (6). Particularly, T cell inflammation in tumors was associated with tumor chemokine expression, particularly CXCL9, CXCL10, CCL5, CCL4, CCL3, and CCL2. T cell attracting chemokines can be produced by a variety of cell types, including tumor cells, dendritic cells (DCs), and macrophages (6–9). The importance and relative contribution of each cell type may depend upon the context and cancer type. However, some tumors grow progressively even when infiltrated with antigen specific T cells, which may be due to immune suppressive feedback and exhaustion of T cell responses (10,11). T cell activation is tightly controlled and requires initiation signals provided by antigen presenting cells, predominately DCs, such as TCR stimulation, co-stimulatory receptor ligation, and cytokine support. Sustained $CD8^+$ T cell responses against tumors are associated with DC supportive niches within the tumor bed, and patients experiencing progressive disease exhibit breakdown of these niches (12). Moreover, DC activation phenotypes, as measured by DC gene signatures, positively correlate with the T cell-inflamed state as well as response to inhibition of the PD-1/PD-L1 pathway (13–15) suggesting a priority need in the field to further understanding of how DCs populate tumors and how to activate DCs to facilitate anti-cancer immunity.

Dendritic cell sub-sets and maturation

Dendritic cells arise from a bone marrow derived DC specific pre-cursor cell (pre-cDC) and depend upon factors such as FMS-like tyrosine kinase 3 ligand (Flt3L) and granulocyte-macrophage colony-stimulating factor (GM-CSF) for their development. DC ontogeny and classification has been thoroughly reviewed by other authors (16–18) and here we will focus only on key DC functions and subtypes. Pre-cDC seed tissues and proliferate to form peripheral DC networks. DCs can be resident within lymphoid organs, or they can surveil peripheral tissues and blood. Inflammatory conditions, including cancer, enhance DC accumulation within tissues from bone marrow sourced pre-cDCs (19). DCs endocytose material from their environment, and if appropriate stimulatory triggers are present, such as pattern recognition receptor (PRR) ligation, DCs mature and transition from antigen sampling to antigen presentation functions. Once mature, DCs upregulate surface expression of the chemokine receptor CCR7 and are attracted towards the CCR7 ligand CCL21 (produced by lymphatic endothelium) to migrate from peripheral tissues to T cell zones of local draining lymph nodes (20). DCs traffic from tissues to draining lymph nodes in the steady state, though when tissues are inflamed DCs traffic in greater numbers. Homeostatic DC migration promotes immune tolerance, in contrast DCs migrating in response to inflammation engender T cell immunity. This is likely due to the upregulation of inflammatory cytokines and co-stimulatory molecules in inflammation matured DCs, signals which are not present on steady state migrating DCs (18).

There are multiple sub-classifications of DCs – which expand further with enhanced profiling approaches (21,22), however these can broadly be grouped into conventional DC type 1 (cDC1), conventional DC type 2 (cDC2), and plasmacytoid DCs (pDCs; Table 1). An additional subset of DCs, monocyte-derived DC, have been described to arise during inflammation and promote context-dependent differentiation of CD4+ T cells. The role for these cells relative to cancer immunotherapy is unclear however and will not be discussed further here. cDC1 are the DC sub-set most well known for their ability to cross present antigens to stimulate $CD8^+$ cytotoxic T cells. These DCs express specialized antigen presentation pathways which allow exogenous cross-presented antigens to be processed and presented on major compatibility complex class I (MHC-I) molecules on the DC's surface (23). These cells express CD11c, MHC II, CD8α, XCR1, CLEC9a, CD24, and CD103. In humans, cDC1 also express CD141. cDC1 development depends upon the transcription factors IRF8, ID2, and BATF3, and loss of these transcription factors eliminates this DC subtype (24,25). Mechanistically, BATF3 maintains activation of IRF8 to specify cDC1 lineage commitment, as transgenic overexpression of IRF8 can rescue cDC1 development (26). In contrast to cDC1, cDC2 potently stimulate $CD4^+$ T cell responses. These cells express CD11c and MHC II, and have surface CD11b, Sirpα, and CD301b (27). CD1c is a marker of cDC2 in humans, however mice lack CD1c genes. cDC2 function and development requires the transcription factors IRF4, RBPJ, KLF4, and RELB (18,27). pDCs are major producers of type I interferon when activated through TLR7 or 9, although identification of the Axl^+ $Siglec6^+$ DC (asDC) subpopulation has called the T cell stimulatory ability of pure pDCs into question (22). pDCs require the transcription factors TCF4 (E2–2), IRF8, and RUNX1 for development. These cells express CD11c and MHC II, and they can be distinguished by B220, Siglec-H, CD317, CD123, and CLEC4C in humans.

pDC are present in blood and lymphoid organs, and can sometimes be found in tissues. In the setting of viral infection, pDC are known to augment $CD8^+$ T cell responses through type 1 interferon activation of cDC1(28), though this mechanism is unexplored in cancer.

Impact of Tumor Intrinsic Signaling on DC Exclusion and Infiltration

Analysis of T cell-inflamed melanomas demonstrated positive correlation with cDC1 gene expression signatures, indicating that the degree of tumor T cell infiltration is strongly tied to cDC1 presence within tumors (13). In contrast to the hypothesis that only overall antigenic load dictates ICB response, it seems that the recruitment and activation status of tumor DCs, in particular cDC1, factor strongly into tumor T cell-inflammation. In support of this, melanoma cell intrinsic secretion of CCL4 can attract cDC1, although this can be blocked by activated β-catenin signaling (29). Studies of hepatocellular carcinoma have also connected the β-catenin pathway with cDC1 tumor infiltration and anti-PD-1 response (30). Indeed, activated β-catenin is associated with non-T cell-inflamed tumors across a range of cancers (31,32). Inhibition of tumor DC recruitment appears to be a dominant mechanism of tumor intrinsic β-catenin activation, though it is unclear whether β-catenin activation has diverse signaling effects across cell types. Tumor intrinsic mutations that strongly alter host immune parameters argue for a cancer cell dependent mechanism of DC recruitment to tumors.

Many tumor cells are genomically unstable which results in the activation of cell intrinsic DNA sensing pathways such as the STING pathway (33). Tumor cGAS/STING is induced by DNA damage, notably that seen in the context of irradiation (34) (35). This pathway is activated upon double stranded DNA (dsDNA) binding to cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) synthase (cGAS). cGAMP then functions as a second messenger and binds STING to activate downstream signaling (36). This triggers interferon response genes and production of CCL5, which can attract cDC1s (37). Extracellular tumor DNA, or cGAMP can activate tumor DCs and initiate T cell responses in the draining lymph node (34,38,39). Tumor cell loss of *LKB1* is associated with poor T cell infiltration and non-response to ICB therapy (40,41), and correspondingly STING signaling pathways can be inhibited by *LKB1* loss. This blunted T cell recruitment to tumors may explain why *LKB1* mutant tumors respond poorly to ICB (42). STING activity is regulated by several proteins notably including the DNA exonuclease *Trex1*(35), which degrades cytosolic DNA substrates that activate cGAS/STING, or via viral proteins that bind directly to STING (43). Further mechanisms of cGAS/STING pathway inhibition will likely emerge and blockade of these may represent therapeutic strategies to induce type I interferon.

Downmodulation of tumor suppressor genes and oncogene expression are now frequently associated with immune exclusion phenotypes, though at this point only β-catenin activation has been mechanistically tied to cDC1 biology (44). Absence of *PTEN* leads to decreased T cell infiltration in melanoma with levels of CXCL10 transcripts decreased in *PTEN* mutant tumors (45). Emerging evidence demonstrates that *IDH1* mutations are strongly correlated with non-T cell inflamed tumors and reductions in factors such as CXCL10 (46,47). The oncometabolite R-2 hydroxyglutarate (R-2-HG), produced by mutant *IDH1*, has also been linked to direct metabolic suppression T cell function (48). DC presence and activity has not yet been assessed in mutant *LKB1*, *PTEN*, or *IDH1* tumors. It will be of substantial interest

to learn whether lack of DCs mediates the non-T cell-inflamed tumor microenvironment in these tumors.

Other mechanisms also likely influence cDC1 recruitment noting that NK cells are primary producers of the cDC1 attractive chemokines CCL5 and XCL1 (49), and the DC differentiation factor Flt3L (14). NK cells precede cDC1 recruitment in some models suggesting that molecular mediators controlling NK accumulation within tumors could be important determinants of cDC1 infiltration. Tumor cell derived prostaglandin E_2 (PGE_2) can inhibit both NK and cDC1 recruitment (50), leading to a non-T cell-inflamed tumor microenvironment. Oncogene influence on NK cell responses is not well described though DNA damage responses within tumors are also known to upregulate NK activating ligands, suggesting that tumor intrinsic features could drive NK activation and recruitment (51).

Alternatively, tumor alterations have been identified that promote T cell-inflamed tumors. Exacerbating tumor intrinsic nucleic acid sensing, via deletion of the double stranded RNA (dsRNA) binding protein *Adar1,* leads to activation of the PKR and MDA5 cytosolic dsRNA sensing pathways, type I interferon induction, and enhanced response to anti-PD-1 (52). In this setting, tumor intrinsic type I interferon production is independent of RIG-I, another cytosolic dsRNA sensor, however tumor cell intrinsic RIG-I has been implicated in anti-CTLA-4 response, and combining anti-CTLA-4 with RIG-I agonist could enhance anti-tumor responses through cDC1 cross-presentation of tumor antigens (53). *TREX1* knockdown in irradiated tumor cells led to enhanced levels of cytosolic DNA that rendered tumor cells more immunogenic through activating the cGAS/STING pathway (35). Loss of function of *PBRM1* in murine melanoma sensitizes tumor cells to interferon γ and T cell killing (54), likewise *PBRM1* loss of function in clear cell renal cell carcinoma patients was associated with response to ICB therapy (55).

Collectively, these studies suggest a model where tumor intrinsic handling of innate immune pathways, in particular nucleic acid sensing pathways, plays a critical role controlling tumor immunogenicity through downstream recruitment and activation of DCs. These responses are then critical for initialization of the T cell response and the T-cell inflamed tumor state (Figure 1).

DCs Induce and Maintain Anti-Tumor T Cell Responses

Beyond the association of DCs and the T cell-inflamed tumor microenvironment, the presence of the Batf3 transcription factor within DCs is becoming apparent as a necessary condition for anti-cancer immunity. This has been emphasized by *Batf3* murine knockout systems which manifest with cDC1 deficiency (25). *Batf3* deficiency prevents spontaneous immunogenic tumor regression and impacts on therapeutic efficacy of many types of cancer immunotherapy including but likely not limited to anti-PD-1/L1 response, adoptive transfer T cell therapy, and tumor specific $CD8^+$ T cell responses (25) (9) (56) (57) (58). Specific dissection of cDC1 function has identified that cross presentation defective mouse strains, lacking Wdfy4 or Sec22b, still retain cDC1 but these cells are incapable of inducing $CD8^+$ T cell responses to reject tumors (59,60). cDC1 deficiency in *Batf3* knockout results in similar findings as $CD8^+$ T cells are not primed effectively and produce far less IFN-γ compared to T cells primed from wild-type DCs (58). cDC1 are also important T cell chemoattractors to

the tumor microenvironment through their production of CXCL9 and CXCL10, though it is unclear if cross-presentation is required in this setting (9,61). CXCR3, the receptor for CXCL9 and CXCL10, is expressed by $CD8^+$ T cells and is required for anti-PD-1 therapy in murine models (8). Anti-PD-1 responsive mouse tumors such as MC38 and MCA1956 had substantially higher CXCL9 and CXCL10 producing DCs compared to anti-PD-1 resistant models such as B16F10 and AT-3, and patients responding to anti-PD-1 had higher induction of these chemokines (8).

cDC1 also provide cytokine support to T cells assisting in their effector functions. IL-12 is a well-known cDC1 produced factor that can drive $CD8^+$ T cell cytolytic activity and secretion of IFN-γ (62,63). Supplying exogenous IL-12 intratumorally in combination with a T cell agonizing CD137 antibody results in durable tumor rejection in MC38 murine models, however this effect is lost in *Batf3* knockout mice (58). Direct administration of IL-12 alone is sufficient to regress tumors in wild-type mice (64), suggesting that T cell priming by Batf3 dependent cDCs is required for response to IL-12 and that T cells are stimulated by IL-12. This is further supported by the finding that tumor infiltrating T cells must receive both T cell stimuli and IL-12 to upregulate IFN-γ production. Specific T cells, and the degree to which they are exhausted, responding to IL-12 are unclear, though T cells isolated from mouse and human tumors can respond to IL-12 (63). IL-12 can drive $CD8^+$ T cells to short lived effector cell (SLEC) fates in models of infectious disease, and in this setting IL-12 can be supplied by non-antigen presenting bystander DCs (65).This could possibly be relevant in cancer as compartmentalized models of DC function have been proposed, but these models remain to be tested.

T cell engagement can occur locally in the tumor microenvironment, or in the context of the lymph node after tumor antigen bearing DCs migrate. cDC1 migrating from the tumor are the major antigen carriers that initiate $CD8^+$ T cell responses (66), however some important differences exist between studies. For example, migratory cDC1 have been shown to carry antigen to the B16 melanoma draining lymph node (57), however both cDC1 and cDC2 have also been shown to traffic antigen to the lymph nodes in other systems (67). Aggregation of evidence strongly supports that migratory DCs in cancer, as the mature DC, are the most efficient at stimulating T cell responses (57,66–68). This is in contrast to viral infection mechanisms that demonstrate antigen handoff from migratory DC to resident DC, with resident DC as the T cell stimulatory population (69,70). It is possible that the lack of strong inflammatory triggers, which are present in viral infection, in cancer prevents antigen handoff mechanisms that would otherwise amplify the immune response. Likewise, augmenting tumor nucleic acid sensing pathways, pathways which also serve anti-viral function can give stronger inflammatory triggers and render tumors immunogenic.

To date, evidence suggests a dominant role for cDC1 in anti-tumor immunity, however tumors are also frequently infiltrated by cDC2. These cDC2 are best able to initiate $CD4^+$ T cell responses upon migrating to the lymph node. T regulatory cells (T_{reg}) restrain cDC2 anti-tumor responses that activate $CD4^+$ T cells (67) and T_{reg} can inhibit DC maturation while hampering migration to draining lymph nodes. Removing this suppression enables IFN-γ producing $CD4^+$ T cells to accumulate in the tumor microenvironment and is independent of $CD8^+$ T cells, suggesting that IFN-γ responses may provide the dominant

anti-tumor effect (71) (52). Tumors can also be shaped by MHC II neoantigens (72) as tumor cell expression of both MHC I and MHC II neoantigens elicited strong anti-tumor immunity. In this instance the $CD4^+$ T cells assist in $CD8^+$ T cell priming and maturation. Abscopal anti-tumor effects were not seen unless the tumor had expression of both neoantigens, suggesting that local $CD4^+$ T cell activation in the tumor site, or draining lymph node, is required for a tumor immune response. These data imply that cDC2, which initiate $CD4^+$ T cell responses, can provide anti-tumor functions in some settings.

Therapeutic Agonism of DCs

Modulation of DCs can be approached via a variety of methods, including but not limited to targeting of innate pattern recognition receptors, supplying DC growth factors, and agonizing cell surface receptors. Modulation strategies presented here are not meant to be an exhaustive list, but rather a general overview of recent attempts to activate anti-tumor DC responses. Diverse methods of therapeutic DC cancer vaccination have been attempted over the past 25 years. Longer summaries of such approaches have been previously reviewed (73) (74) (75).

Agonism of toll like receptors (TLRs) drives pro-inflammatory gene programs that can engender anti-tumor immunity. The endosomal TLRs (TLRs 3, 7, 8, and 9) make particularly attractive targets as these receptors naturally sense foreign nucleic acid patterns such as dsRNA, ssRNA, and unmethylated CpG and trigger type 1 interferon responses. Based on current understanding of interferon response and tumor immunogenicity, these pathways are attractive therapeutically toward recapitulating microenvironmental features of T cell-inflamed tumors. Agents such as Poly I:C (TLR3 agonist), NKTR-262 (TLR7/8 agonist), CMP-001 (TLR9 agonist) and Tilsotolimod (TLR9 agonist), among others, are in clinical development and testing. Clinical trial biomarker investigation of these agents has suggested increases in intratumoral interferon responses, T cell chemokines and tumor infiltrating $CD8^+$ T cells (76–78).

Targeting the cGAS/STING pathway through STING agonism is another emerging therapeutic approach. Host DC uptake of tumor DNA induces a STING dependent interferon response that is needed for anti-tumor immunity (38). Agonizing this pathway pharmacologically could be an approach to elicit anti-tumor dendritic cell responses (36). Clinical data has been disclosed for ADU-S100 and MK-1454 (79) demonstrating the induction of systemic type I interferon response, however little intra-tumoral biomarker data has been released. In general, the intra-tumoral injection approaches pursued to date may require optimization to improve clinical efficacy, though randomized phase II and phase III trials have been launched for TLR9 and STING agonists in combination with ICB.

Several other intriguing approaches are also on-going in clinical trials. Combining poly I:C activation with CDX-301 (human Flt3L) and radiotherapy in an approach termed "*in-situ* vaccination" has been described as demonstrating abscopal anti-tumor responses in indolent non-Hodgkin's Lymphoma with effect mediated by increased tumor T cell infiltration and tumor cross presenting DCs (80). Other dsRNA detection pathways like the cytosolic RIG-I sensor can be activated using the synthetic RNA oligonucleotide MK-4621. Phase 1/2 trials are underway with this agent and have demonstrated tolerable safety profiles and could

enhance interferon gene expression in tumors (81). Targeting of CD40 via agonistic antibodies has demonstrated limited single agent activity to date, however emerging evidence suggests that effective CD40 agonism requires antibody Fc engagement of Fcγ receptor 2b. Newer CD40 agonist antibodies, such as APX-005M and 2141-V11, with enhanced Fcγ receptor 2b affinity show improved CD40 crosslinking and activation of DCs in pre-clinical models, and are currently undergoing early stage clinical trials (82).

Future for DC Agonism in Cancer Immunotherapy

Further elucidating the biology surrounding DC control of T cell immunity will be critical for selecting rational combination therapies moving into the future. The highest unmet need in cancer immunotherapy may be to overcome the non-T cell-inflamed tumor microenvironment and facilitate antigen-specific T cell recruitment. Early clinical trials of DC agonists, such as those above, have yet to consistently show such effects and novel approaches in delivery or drug development may be necessary to accomplish this. An unmet need also continues to exist in T cell-inflamed tumors that do not response to immunotherapy. For example, in non-small cell lung cancer the response rate to anti-PD-1 in patients with tumors that are $PDL1^{+}$ > 50% remains only approximately 45%(83).

Recent studies have indicated that neoadjuvant checkpoint inhibitor treatment can produce enhanced anti-tumor T cell responses compared to adjuvant therapy, with more clonal and diverse tumor T cell infiltrates in the neoadjuvant setting (84,85). T cell responses to checkpoint inhibition can be rapid, and response can be seen in blood and normal adjacent tissue (86) (87). T cell clonotyping analysis also suggests that novel T cell clones not previously seen in the tumor can be observed following checkpoint inhibition (88) (85). It is likely these peripherally stimulated T cells are activated via DCs – possibly within tumor draining lymph nodes. Blockade of PD-1/PD-L1 can also enhance priming of naïve T cells (15), suggesting that these therapeutics do not solely act on pre-existing T cell clonotypes. Several of these studies also associated tumor T cell inflamed gene signatures with therapeutic benefit (84–86). DCs can have multiple roles in this setting, from initiating T cell expansion, to guiding T cell entry and effector function within tumors. It will be important to examine anti-tumor T cell clonalities in response to DC directed therapeutics, and the location of tumor antigens to understand where T cell re-invigoration occurs. Antigen location should also be taken into account when using DC agonist therapy. For example, peritumoral dosing of CD40 agonist antibodies drives stronger anti-tumor responses compared to systemically delivered agonist, and CD40 agonist delivered to an irrelevant tissue site failed to generate anti-tumor responses (89). Determining whether the application of DC agonists is optimally to the tumor or whether cross-presentation in the draining lymph nodes is operative may impact on combination partner selection. If this is indeed the case, a reasonable hypothesis may be entertained that optimal ICB combination therapy may include anti-CTLA-4. Further, combinations of multiple DC agonists may be necessary to optimally prime tumors for ICB response (53).

Effective cancer immunotherapy has been strongly associated with the presence of the T cell-inflamed tumor microenvironment and DC activation appears to be a primary driver of this phenotype. Conversely a major mechanism of resistance appears to be the lack of T cell-

inflammation, raising agonism of DCs to generate type I interferon, in combination with ICB, as a priority approach. Multiple molecular targets are being actively explored however novel drug delivery approaches may be necessary. Many in the field have proposed to convert cold tumors to hot or make hot tumors hotter, we will observe with interest whether this simple paradigm can expand the numbers of patients benefiting from cancer immunotherapy over the next several years.

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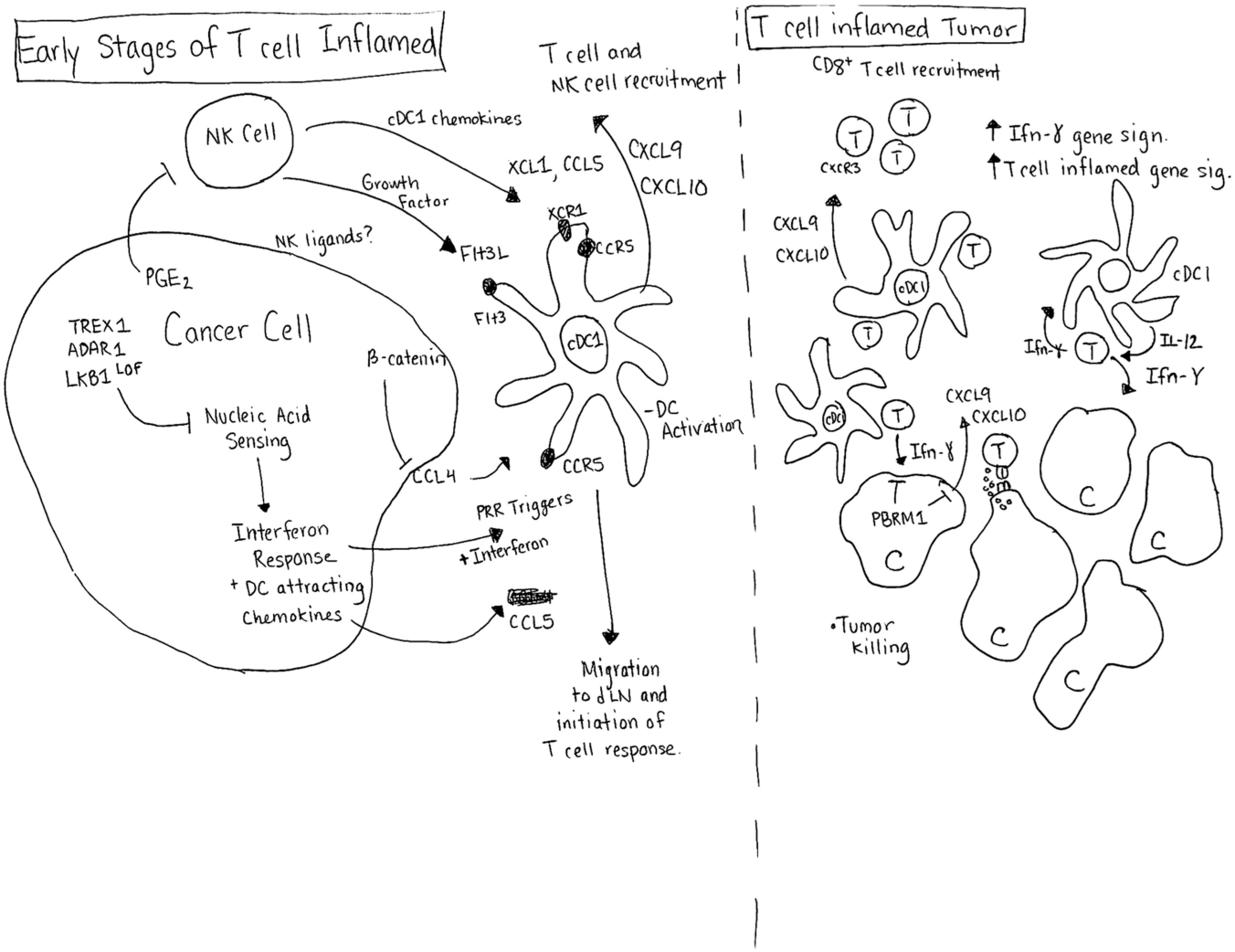

Figure 1 Legend:

Determinants of Tumor Dendritic Cell Infiltration. (Left Panel) Tumor cell intrinsic innate sensing of nucleic acids (both DNA and RNA substrates) induces interferon responses that attract dendritic cells (DC). Blocking innate nucleic acid sensing by limiting activating substrates (ADAR11 – RNA, TREX1 – DNA) or inhibiting STING signaling tempers tumor cell immunogenicity. cDC1 attractive chemokines produced by tumor cells can include CCL4 and CCL5, though production of CCL4 can be blocked by activated β -catenin. Natural killer cells (NK) can also produce the cDC1 tropic chemokines XCL1 and CCL5, and can support DC functions by producing the DC growth factor Flt3L. Tumor cell derived prostaglandin E2 (PGE2) can inhibit NK functions and cDC1 recruitment into tumors. Activation of DCs leads to initiation of anti-tumor T cell responses. (Right Panel) T cell inflamed tumor replete with DCs and cytotoxic T cells. T cell derived interferon γ inhibits tumor cell growth and activates local tumor cDC1 to produce IL-12, and the chemokines CXCL9 and CXCL10. DC produced IL-12 further activates tumor CD8+ T cells, and CXCL9/CXCL10 recruit T cells into the tumor microenvironment.

TABLE 1.

Dendritic Cell Subtypes

DC Type	Cell Surface Markers	Key Transcription Factors	Primary Functions
cDC1	CD11c, MHC II, CD8α (lymphoid resident), XCR1, CLEC9a, CD103, CD141 (human), CD24	BATF3, IRF8, ID2	Cross presentation of antigens to activate $CD8^+$ T cell mediated immunity, T-helper 1 type immune response, Secretion of IL-12, CXCL9 and CXCL10 mediated T cell recruitment
cDC2	CD11c, MHC II, CD11b, Sirpα, CD301b, CD1c (human)	IRF4, RBPJ, KLF4, RELB	$CD4^+$ T cell activation, Humoral immune responses, Allergic immunity and T-helper 2 type immune response
pDC	$CD11c^{low}$, MHC II^{low}, B220, SIGLEC-H, CD317, CLEC4C (human), CD123	TCF4 (E2-2), IRF8, RUNX1	Type 1 interferon production, Limited antigen presentation to T cells, Augmenting DC responses through interferon signals

DC = dendritic cell