Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth most common cause of death from cancer worldwide, with a poor 5-year survival rate of 6%. Patients with PDAC poorly respond to chemotherapy, radiotherapy, or immunotherapy. Emerging evidence linking such poor prognosis and immune evasion compels us to explore the mechanisms behind immunosuppression in pancreatic tumor microenvironment (TME). This review introduces several potential mechanisms focusing on resident cells in pancreatic TME. We have also summarized recent published studies (1-25) in this field in Table (26-50) (http://fp.amegroups.cn/cms/apc.2019.06.04-1.pdf) (51-55).

Pancreatic cancer microenvironment

PDAC is characterized with accumulation of a desmoplastic stroma, which is composed of a plethora of cellular and acellular components, including fibroblasts, immune cells, pancreatic stellate cells (PSCs), endothelial cells, extracellular matrix, and soluble proteins such as cytokines and growth factors (56-59). These components constitute an immunosuppressive TME and up to 90% of the tumor bulk, function as an important mediator of therapy resistance and might be responsible for the failure of immunotherapy (60). While immune cells are abundant within the stroma, they mostly belong to immunosuppressive subsets such as tumor-associated macrophages (TAMs), tumor-associated...
neutrophil granulocytes (TANs), regulatory T cells (Tregs), or immature myeloid cells/myeloid-derived suppressor cells (MDSCs) (61–63). These cells are recruited by tumors as an escape mechanism from immune surveillance, and they interact with other stromal components to create an immunosuppressive network (64). Conversely, anti-tumor immune cells like DCs, NK cells, and CD8+ T cells are relatively few and their anti-tumor effects are generally impaired. For example, majority of CD8+ T cells in pancreatic TME express high level of immune checkpoint receptors that significantly limit their cell-killing effects (65).

One study has shown that adipocytes contribute to tumor microenvironment of obese pancreatic cancer patients. Hijacked adipocytes or tumor cells produce IL-1 to activate pancreas stellate cells (PSCs), and then the activated PSCs (aPSC) secrete IL-1 to recruit TANs who subsequently activate PSCs and mediate the tumor immunosuppressive microenvironment (66).

The PDAC microenvironment is glycolytic compared to surrounding tissue and associated with poor outcome in PDAC (67). Increased lactate in the extracellular environment was exported by monocarboxylate transporter 4 (MCT4) from tumor cells who obtain energy in unique metabolic ways such as aerobic glycolysis, also known as the “Warburg effect”. The resultant lactate can limit T-cell effector functions, as this subset of immune cells is dependent on aerobic glycolysis (68). In contrast, macrophages and Tregs are able to use fatty acid oxidation to survive in a low-glucose environment (69,70). Additionally, the accumulated lactate at high concentration can skew macrophages towards the anti-inflammatory, tumor-promoting phenotype (M2-type) (71).

Pancreatic cancer cells

To escape attacks from the immune system, pancreatic cancer cells adaptively adjust themselves to the microenvironment around. For example, cancer cells downregulate the expression of antigen presenting molecules including major histocompatibility antigen (MHC) class I, B7-H5, and Fas receptor to diminish cell-mediated immunity and intensify the expression of Fas ligand, which induces apoptosis of activated antitumor cytotoxic T cells (12,72–75). Further, pancreatic ductal epithelium upregulates the expression of adhesion molecule L1CAM (CD171), which enriches Tregs in TME to correlate malignant progression (50,76). Soluble ULBP2 (sULBP2), a ligand of NKG2D receptor, was also upregulated in pancreatic cancer to decrease NK cytotoxicity towards tumor (4). Moreover, Hinz et al. found that transforming growth factor-2 (TGF-β2) induced Foxp3 (a transcription regulator) expression in pancreatic carcinoma to mediate immune privilege by suppressing proliferation of activated cytotoxic T cells, suggesting that pancreatic cancer cell may mimic Treg function in immune evasion (6). Similarly, focal adhesion kinase (FAK) was reported to correlate with high level of fibrosis and poor CD8+ cytotoxic T cell infiltration (7). B7-H4 is highly expressed on pancreatic cells disregard of the presence of pancreatic cancer, and it inhibits T cell proliferation, filtration, and interleukin-2 production (77–79). It was reported that tumor-associated Tregs can stimulate macrophages to secrete IL-6, subsequently activate STAT3 which binds to the promoter of B7-H4 gene, leading to enhanced B7-H4 expression in tumor cells, antigen presenting cells (APCs), or other microenvironment-supporting cells (80–82).

It was reported that pancreatic cancer cells can secret TGF-β via activating Smads (83,84) and facilitate immature dendritic cells turning into TGF-β-secreting cells (85,86). TGF-β is a multifunctioning cytokine involved in nearly all pivotal steps of neoplasia (87). In early pancreatic tumorigenesis, TGF-β acts as a suppressor due to its growth-inhibitory effect on epithelial cells, but it appears to promote tumor progression in advanced disease (55) as it promotes the proliferation of PSCs and the recruitment of CD4+ CD25+ FoxP3+ Tregs and also directly affects CD8+ cytotoxic T lymphocytes (CTLs) (65,88). According to reports, TGFβ inhibits CTL activity and differentiation through several suppressant genes implicated in anti-tumor immune response including Granzyme B (89), which is an anti-tumor serine protease found in CTL-associated cytotoxic granules (90,91). Patients with loss of SMAD4 are appropriate target population for using TGFBR-inhibition therapy since those patients will not benefit from growth-inhibitory effects of TGF-β (55). In addition, tumor cells can also secrete IL-1 to induce intratumoral DCs to produce CCL22, which was known to recruit Treg into TME (11).

Cancer cells are also capable of transforming their metabolism in TME to escape the attacks from immune system (92). For example, increased expression of indoleamine-2,3-dioxygenase (IDO) depletes tryptophan which is an important amino acid routinely functions in immune system cells including NK cells, cytotoxic T cells, and T effector (Teff) cells in PDAC (53,93,94). MMP-9
Pancreatic stellate cells (PSCs)

Increasing evidence demonstrates that the interaction between aPSCs and PDAC cells makes a difference in the development of PDAC. Through producing high level of growth factors, cytokines, chemotactic factors and excessive extracellular matrix (ECM), PSCs create desmoplasia and a glycolytic microenvironment that promote the initiation, development, invasion, metastasis, immune evasion, and chemoradiotherapy resistance of PDAC (97). In response to pancreatic injury, stress, inflammation, resident PSCs are converted into an activated myofibroblast-like phenotype to express α-smooth muscle actin (α-SMA), and synthesize ECM proteins to form fibrous tissue (98,99). The aPSCs are the main source of cancer-associated fibroblasts (CAFs). However, the difference between CAFs and aPSCs is still under debate (100).

PSCs play an important role in mediating immune escape in pancreatic cancer. The rigid ECM components (such as collagen and fibronectin) induce Rho-associated coiled-coil kinase-dependent activation of FAK1. In turn, FAK1 tyrosine kinase regulates T cell survival, antigen sensitivity, cytokine production and migration, to significantly contribute to immunosuppression (7). Known to be produced by CAFs, fibroblast activation protein-α (FAP-α) and βig-h3 disrupt anti-tumor immunity, leading to immune escape and tumor growth (43,45).

PSCs also secrete plentiful soluble cytokines that conduce to T cell exhaustion and dysfunction. FAP+ PSCs are the only tumoral source of chemokine (C-X-C motif) ligand 12 (CXCL12, also named stromal-derived factor-1, SDF-1) that limits cytotoxic T cell trafficking, prompts macrophages’ differentiation into M2-type, and recruits TANs and MDSCs to the tumor site (101). Meanwhile, CXCL12/SDF-1 bound to PDA cells inhibits T cell access, leading to reduced immune responses (40,102). A recent study showed that REG3β expressed and released by healthy cells in the peritumoral region far from microenvironment could activate CXCL12/CXCR4 signaling cascade and interfere with the intercellular communication inside the tumor mediated by extracellular vesicles, resulting in macrophage phenotype alteration and tumor cell migration (103). In PDAC, activated PSCs, TAM, Tregs and mast cells can inhibit DC activation by producing high level of immunosuppressive cytokines such as IL-10 and TGF-β (99,104,105). Similarly, interleukine-6 (IL-6), another versatile PSCs/MDSCs derived cytokine, inhibits cytotoxic T lymphocyte (CTL) anti-tumor immunity by multiple mechanisms, including impairing Teff cell trans-endothelial migration, activation of Treg cells or TAMs, and disrupting the balance of Treg/Teff activities (44,106). Other excessive PSCs-derived suppressive cytokines such as VEGF, granulocyte-macrophage colony-stimulating factor (GM-CSF), PGE2, and MCP-1, also primarily contribute to immune escape and therapeutic resistance of PDAC (107,108). Furthermore, a recent study has demonstrated that galectin-1 is also secreted by activated PSCs, and it modulates Teff cell activation, proliferation, and apoptosis, holds T cells in an anergic state, and breaks the cytokine secretion balance toward a T helper type 2 (Th2) immune response (41).

Recent studies show that CAFs are capable of attracting and sequestering CD8+ T cells in the extratumoral compartment, which dampens T cells’ contact with and cell-killing effect of tumor cells (109). Depletion of CAFs abolishes immune suppression (110,111), enhances anti-tumor activity of anti-CTLA-4 as well as anti-PD-L1 (40,46), but also leads to infiltration of Tregs and induction of more aggressive tumor phenotypes (46,112). PEGylated hyaluronidase-degraded hyaluronic acid increases the intratumoral delivery of chemotherapy drugs (57) and improves effective tumor infiltration by CTLs (113) but it was restricted to patients with high hyaluronic acid level in tumor (114). Cyclosporine (M-CPA)/paclitaxel (PTX) was recently reported to restrain tumor cell proliferation and increase intratumoral vasculature density without concomitant infiltration of Tregs or MDSCs (47).

Myeloid cells

Tumor-infiltrating myeloid cells including CCR2+ TAM and CXCR2+ TAN, known as important mediators of immune evasion (115), secrete high level of IL-10 to enhance Treg and Th2 activation and expansion, and they can be targeted by small molecule inhibitors of CCR2 (CCR2i) and CXCR2 (CXCR2i) (116-118). Combined targeting of CCR2+ TAM and CXCR2+ TAN has the benefit of avoiding compensatory increase of counterpart compared with either TAM or TAN targeting alone. This is expected to result in a
significantly influx of CD8\(^+\) tumor-infiltrating lymphocytes with a remarkable decrease of Tregs to infiltrate (60,119).

Depending on dominant signals around, macrophages can adopt an alterable functional status (24). When stimulated by bacterial products such as lipopolysaccharide (LPS), Th1 cytokines, IFN-\(\gamma\) or TNF-\(\alpha\), macrophages become immunostimulatory (M1) with high expression of inducible nitric oxide synthase (iNOS), CD80, CD86, MHCII proteins, and TNF\(\alpha\) to exert their tumoricidal effects (120,121). On the contrary, in response to Th2 cytokines, IL4, IL10, IL13, or immunocomplex (IC), macrophages acquire an alternatively immunosuppressive status (M2) that express arginase 1, CD206, and low amounts of MHCII (120,122). TAMs often have characteristics of both M1 and M2 and the phenotype of TAMs may change during tumor development (123). TAMs may play an M1-like phenotype role in the early stage of carcinogenesis, and gradually convert into an M2-like phenotype when tumors start to invade and metastasize (124). Along with tumor progression, Tams with M1-like phenotype, M2-like phenotype, or with co-expressed markers of both M2 and M1 macrophages exist in pancreatic TME and a higher M2:M1 ratio correlates with a poor prognosis (125,126). Although majority of TAMs tend to be M2-type, their biological activity can be redirected (127). For example, CD40 agonist, paclitaxel, low-dose \(\gamma\) irradiation, inhibitor of receptor-interacting protein kinase 1 (RIP1) or RIP3, or disruption of the dectin 1-galectin 9 axis are all shown to redirect macrophages from M2-type to M1-type with their respective effects, in consequential or parallel manner (22,23,25-27,128-130).

MDSCs (CD11b\(^+\)), the precursors of macrophage, neutrophil and dendritic cells, are regarded as another inhibitory population of myeloid cells. Accumulated MDSCs and their enhanced function are induced by soluble mediators in TME, including IFN-\(\gamma\), TNF, and GM-CSF (131-136). Expansion of MDSCs was shown to be further driven by cytokines such as TGF-\(\beta\), IFN-\(\gamma\), G-CSF, GM-CSF, VEGF, IL-1\(\beta\), IL-6, IL-10 and CCL12 in PDAC (137). There was report that cytokines inducing MDSCs via acting on a conjunct molecular pathway and the immunosuppressive activity of both tumor-induced and bone marrow-derived MDSCs are completely dependent on the C/EBPbeta transcription factor (138).

MDSCs exhibit a profound capacity to suppress T cell proliferation and activation in a dose-dependent manner and attenuate functional differentiation of tumor-specific CD4\(^+\) T cells into effector TH1 cells via IL-6 production to facilitate tumor progression (106). Depletion of CD11b\(^+\) MDSC cells downregulates the expression of PD-L1 in tumor cells, resulting in a significant infiltration of CD8\(^+\) T cells and a decrease of immunosuppressive Tregs infiltration, leading to effective inhibition of pancreatic tumor growth in a CD8\(^+\)T-dependent fashion (17). Recently, neutrophil-like CD13\(^{high}\) MDSCs are found to suppress anti-cancer T cell responses via expression of arginase-1 and correlate with poor prognosis of PDAC patients (139). Inhibition of cyclooxygenase-2, PGE2-mediated arginase, or phosphodiesterase-5 was shown to downregulate arginase-1 in murine MDSCs and led to an effective tumor control (19,20).

**Tregs**

Natural CD4\(^+\)CD25\(^+\) Tregs and Foxp3-transduced CD4\(^+\) T cells suppress naïve T-cell proliferation in vitro in order to maintain immunologic tolerance (140). The forkhead transcription factor Foxp3 is a key molecular marker to identify Treg function and is the only definitive marker of CD4\(^+\)CD25\(^+\) Treg (140,141). Apart from naturally occurring Tregs generated from the thymus, adaptive Tregs as negative regulators of anti-tumor cytotoxic T cells recognized, as these cells predominate in infections and tumor such as pancreatic adenocarcinoma and associate with poor prognosis in PDAC (142,143). Tumor cells recruit Tregs throughout an epithelial-to-mesenchymal (EMT) process by expressing L1CAM and secreting mediators including C-C motif chemokine ligand 2 (CCL2) and CCL22 (11,39,50). Tregs inhibit T-cell production of IFN-\(\gamma\) and IL-2 as well as their cytotoxic function, resulting in impediment to naturally occurring anti-tumor immunity (143).

Anti-CD25 mAb can enhance CTL responses and diminish pancreatic tumors in a CD8\(^+\) T cell-dependent manner (49). However, this strategy may cause immune dysfunction since CD25 is not a specific Treg marker. Recently, low-dose CpG TLR9 agonist improved ISOCOM tumor vaccine function by breaking Treg-mediated immunosuppression (49,144).

**CD4\(^+\) T cells**

CD4\(^+\) T cells are effector helper cells that can differentiate into three major subtypes with distinct function, playing an important role in immune response via releasing dissimilar inflammatory cytokines. Th1 cells support cellular immunity by selectively producing IL-2, IFN-\(\gamma\) and
TNF-α (145,146). Th2 cells support humoral immunity by producing IL-4, IL-5, IL-6, IL-10 and IL-13 (147). IL-4 and IL-10 are deemed as immunosuppressive factors (108,148). Th17 cells exert a strong pro-inflammatory effect by producing IL-17, IL-21 and IL-22 (149,150). While Th1 cells are assistant to cellular response against tumor cells, Th2 cells are believed to collude with pancreatic cancer cells and a higher Th2:Th1 ratio in tumor correlates with a poorer prognosis in pancreatic cancer patients (42). Emerging evidence suggests that IL-10 and TGF-β facilitate the shift of Th1 into Th2 cell type in vitro (151). Another study demonstrated that pancreatic cancer cells restrict CD4+ T-cell proliferation and migration, and induce IFN-γ production, supporting a role of CD4+ T cells in immune evasion (152).

**CD8+ T cells**

As the main force of tumor cell-killing immune cells, cytotoxic CD8+ T cells recognize specific tumor antigens presented as peptides on MHC class I molecules (153). Unfortunately, they express high levels of immune checkpoint receptors such as PD-1 (65). Strong evidence have proved that a pre-existing anti-tumor CD8+ T cell infiltration is required for therapeutic benefit from ICB and other immunotherapy (154,155). However, once memory T cells are generated, they are able to protect mice upon inoculation with other PDAC tumors since limited mutations shared among the majority of PDAC patients (34).

The prime task of the seesaw battle between tumor and body immunity is to release CD8+ T cells from the suppression of PD-L1. PD-L1 (B7-H1), an important co-suppressive molecule expressed on macrophages and DCs as well as on pancreatic cancer cells, was reported as a negative regulator of T-cell responses. PD-1 interacts with its ligand PD-L1 to maintain self-tolerance and to protect against excessive tissue damage induced by immune responses through downregulating the synthesis and secretion of IL-2, IFN-γ and IL-10 by myeloid DCs and T cells, and thus functions as an immune checkpoint under physiological conditions (156-162). It has been reported that PD-L1 can be upregulated by oncogenes such as AKT and STAT3 (163,164) or by chemotherapeutics like 5-fluorouracil, gemcitabine and paclitaxel via several pathways including the JAK/STAT pathway (165). Further, IFNγ, a proinflammatory cytokine secreted by activated T and natural killer (NK) cells and a vital component of the host cancer immune system (166,167), also acts as a prime inducer of PD-L1 in tumor cells via the MEK/ERK pathway and can be inhibited via suppressing STAT1 (168-171).

With the aforementioned role of immunosuppression, blockade of the interaction between PD-1 and PD-L1 by anti-PD-1 or anti-PD-L1 already demonstrated durable efficacy of tumor suppression in both mouse tumor models and human cancer patients except PDAC (65,172-176). The explicit cause of disabled curative effect remains uncertain. It was reported that anti-PD-1 treatment motivated a compensatory increasing expression of cytotoxic T-lymphocyte-associated protein 4 (Ctda4), which is another immune checkpoint (17). Arlauckas et al. showed that macrophages can remove anti-PD-1 antibodies from T cells (177). Therefore, combination of anti-PD-L1 and other therapies appears logic and attractive for pancreatic cancer. As reported, combination of high-dose radiotherapy with anti-PD-L1 markedly enhanced tumor responses in PDAC cell allografts where radiotherapy induced a large amount of tumor cells sensitive to cytotoxic killing. Further, early anti-PD-L1 therapy prevented the growth of immunosuppressive cells and increased recruitment and activation of T cells (178). Analogously, depleting FAP-expressing cells, Mll1 inhibitors, CXCL12/CXC R4 pathway inhibitors, tocilizumab (anti-IL-6), CD40 agonist, STING agonists, for instance, all acted synergistically with anti-PD-L1 to significantly diminish cancer growth in a CD8+ T-dependent manner (22,40,44,51,65,168).

B7-H5, a new B7 ligand for receptor CD28H to deliver a costimulatory signal to the human T-cell, is downregulated in pancreatic cancer cells, which might partially cripple CD8+ T cells' function (52). Recently, Chen et al. discovered that fibrinogen-like protein 1 (FGL1), a protein that is largely limited to liver and pancreas, was a major immune inhibitory ligand of another immune checkpoint LAG-3 (179,180). FGL1 is highly produced by human cancer cells and it inhibits the activation of antigen-specific T cell as well as NK cells (179,181). While its expression appears to be downregulated in pancreas cancer (179), normal pancreatic tissues may express enough FGL1 to exert its immunosuppression. LAG-3+ cells are frequent in CD3+CD8+ TILs (96.30%) in PDAC (182). Blockade of FGL1-LAG3 may have promising effect on pancreatic cancer. More recently, it was reported that the intrinsic capacity of intratumoral T cells to recognize tumor tissue was rare and variable, suggesting that reactivating intratumoral T cells would benefit from approaches that simultaneously increase the quality of the intratumoral
TCR repertoire (183).

**NK cells**

NK cells, as the first line of defense in the body, play an essential role in the innate immune system and anti-tumor immunity including pancreatic cancer (184). Evidence shows that NK cells not only kill target cancer cells directly without prior sensitization (185,186), but also bind to specific surface ligands expressed on cancer cells, such as MHC class I molecules (187). Interestingly, complete loss of MHC class I will motivate NK cells response, which called the “missing self” response (188). In addition to their ability to kill mAb-coated tumor cells via inducing antibody-dependent cellular cytotoxicity (ADCC), FcR-activated NK cells also release cytokines including IFN-γ, TNF-α, MIP-1α, IL-8, and RANTES to improve antigen presentation, stimulate the chemotaxis of T cells, and suppress tumor cell proliferation (189,190). NK cell function can be enhanced via IL-21 produced by activated CD4+ T cells (191) and impaired via downregulation of specific activating surface receptors (e.g., NKG2D), cytotoxic granules (e.g., Perforin and Granzyme B), natural cytotoxicity receptors (NCR), or upregulation of MMP-9 and Igγ-1 chain C region (54,192,193). Targeting these molecular markers can partially restored NK function and retard tumor growth.

**Dendritic cells**

Dendritic cells (DCs) serve as specific antigen-presenting cells to pick up antigens from damaged tumor cells and then present them with the support of CD4+ Th cells to CD8+ T cells in the lymph nodes, a mechanism named “cross-priming” (153). Tumor-residing CD103+ DC are indispensable to recruit Teff cells into the TME and establish the T cell-inflamed tumor phenotype with a large CD8+ T cell infiltration (35). The establishment of non-T-cell-inflamed tumors may due to deficiencies in T cell priming for lack of cross-presenting dendritic cells, which is believed due to increased CXCL1 in tumors in a c-Myc-dependent manner (34). It was reported that increased IL-10 concentration limited antitumor cytotoxic T-cell responses and activation of NK cells during therapy by suppressing intratumoral DC production of IL-12 (28). One study showed that following three injections of the lipid-protamine-DNA (LPD) nanoparticles loaded with trap genes (IL-10 trap and CXCL12 trap), tumor growth was reduced, prolonged host survival was achieved with significantly reduced immunosuppressive cells such as M2 macrophages, MDSCs, and PD-L1+ cells (28). Some agonists like CpG, ISCOM vaccines, and CD40 agonist could also enhance antigen uptake and antigen processing by DCs (33,36,37,65).

Noting that DCs carrying antigens need to migrate from the tumor to the lymph nodes to activate CD8+ T cells. IL-8 produced by pancreatic cancer cells prevents the journey induced by MIP-3β since DC uniformly express both IL-8 receptors CXCR1 and CXCR2 (38,194). Perhaps for this reason the quantity of DCs was significantly decreased in peripheral blood of PDAC patients (195).

CCL2, a chemokine that dramatically upregulated in pancreatic cancer cells, recruits various immunosuppressive cells such as MDSCs (196). Cooperatively, CCL2 and LCN2 in combination stimulate the generation of immunoregulatory DCs (DCreg), which have suppressive activity due to lowered expression of costimulatory molecules such as HLA-DR (39). DCreg subsequently induces immunosuppressive Treg cells, and eventually impair tumor-specific CTL function (39).

**Perspectives and conclusion**

Overall, pancreatic cancer immunotherapy aims to promote cytotoxic CD8+ T cell recruitment to pancreatic cancer and their killing effects against cancer cells. Low infiltration of CD8+ T cells is primarily due to the physical barriers of tumor stroma and inhibitory cytokines and chemokines within the TME. Lack of TILs’ cytotoxicity may be due to decreased antigenicity in tumor cells, inhibition of immune checkpoints, direct effect of inhibitory cells, or effect of cytokines. It is also possible due to ineffective activation of TILs, because of function limit of DCs and poor specificity among TILs. Strategies to relieve immunosuppression include depleting inhibitory cells or suppressing their function, blocking signal transduction pathways, redirecting the relevant immune cells from pro-tumor status to anti-tumor status, relieving immune checkpoint suppression, and promoting TILs to resist cancer cells.

Although immunotherapy emerges as a promising therapeutic option for pancreatic cancer, it still has not achieved significant and satisfactory improvement on the survival of patients. Crosstalk among various cells forms an intricate network that mediates immune evasion in pancreatic cancer microenvironment. Single therapy to date seems powerless to break through the constraint of immunosuppression, leaving combination therapies a
mission and hope. In consideration of inevitable side effects, identification of specific targets and development of non-overlapping treatments may provide insights to improve efficacy and reduce adverse effects. Finally, thorough understanding of immunosuppression and enhancing of TILs’ anti-tumor specificity and lethality are constant topics and avenues for conquering pancreatic cancer with immunotherapy.

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Footnote

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