Trends in Cancer

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Spotlight

Tumor immune escape by autotaxin: keeping eosinophils at bay

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Secreted autotaxin (ATX) promotes tumor progression by producing the pleiotropic lipid mediator lysophosphatidic acid (LPA). In a recent *Nature Cancer* paper, Bhattacharyya *et al.* show that ATX/LPA signaling suppresses CCL11-driven infiltration of eosinophils into the pancreatic tumor microenvironment to facilitate tumor progression, thus revealing a new ATX-mediated immune escape mechanism and highlighting the antitumor potential of eosinophils.

Thirty years since its discovery as a potent inducer of tumor cell motility, autotaxin (ATX) still has surprises in store, especially regarding tumor immune evasion, as revealed by recent studies. ATX (encoded by *ENPP2*) is a unique phospholipase that is secreted by diverse cell types to convert abundantly available lysophosphatidylcholine into the bioactive lipid lysophosphatidic acid (LPA), which signals through specific G protein-coupled receptors (LPAR1-6) to regulate a plethora of biological functions [1]. Numerous preclinical studies have implicated the ATX-LPAR signaling axis in tumor progression, acting mainly via LPAR1. Yet, the actions of ATX/LPA in the tumor microenvironment (TME) have long remained unclear. Perhaps this is no surprise given that most, if not all, cell types in the TME express multiple LPA receptors, both stimulatory and inhibitory, while tumor-associated ATX originates from heterogeneous cellular sources. This makes the unraveling of ATX/LPA signaling networks in a tumor–immune context a daunting task.

Recent studies have changed the tide by uncovering ATX as a suppressor of T cell antitumor immunity. In brief, tumor cell-secreted ATX activity suppresses the chemotactic migration and tumor infiltration of $CD8^+$ T cells to impede antitumor immunity and tumor control, with a migration-inhibitory role for LPAR6 [2]. Moreover, LPAR5 has emerged as an inhibitory receptor that impairs $CD8^+$ T cell cytotoxicity and immune synapse formation [3]. Additionally, ATX/LPA dampens type I interferon responses and infiltration of $CD8^+$ T cells in metastatic ovarian cancer [4], while an ATX-LPAR5 signaling axis suppresses $CD8^+$ T cells to promote anti-PD-1 resistance in non-small cell lung cancer models [5]. Thus, ATX/LPA signaling repels and paralyzes tumor-infiltrating $CD8^+$ T cells via functionally distinct LPA receptors to prevent tumor cell killing and, thereby, contributes to tumor progression.

The ATX/LPA tale has taken a new twist in a recent study in *Nature Cancer*. Bhattacharyya and colleagues explore how ATX affects immunoregulation in pancreatic ductal adenocarcinoma (PDAC) [6]. PDAC is an aggressive and highly lethal cancer that is characterized by a complex microenvironment and is in urgent need of more effective therapies. The authors found that PDAC cell-derived ATX suppresses the infiltration of eosinophils into the PDAC microenvironment to promote tumor progression. But in this case, ATX/LPA acts indirectly via an autocrine signaling mechanism that downregulates the production of chemokine CCL11 (eotaxin-1) in PDAC cells to keep tumor-associated eosinophils at bay [6]. Eosinophils are myeloid granulocytes that infiltrate solid tumors, where they can exert both anti- and pro-tumor actions, which have been relatively understudied to date [7].

Expanding on earlier work showing that ATX/LPA promotes PDAC cell proliferation and tumor growth [8], Bhattacharyya *et al.* used *Enpp2* loss-of-function approaches and small-molecule ATX inhibition to show that ATX ablation reduces tumor burden and increases apoptotic killing of implanted PDAC cells, which was rescued after restoring ATX expression [6]. The authors went on to perform immune profiling of control and ATX-deficient PDAC tumors. Unexpectedly, T cell infiltration was not significantly affected in the ATX-deficient PDAC setting. Instead, there was a threefold increase in eosinophil abundance. ATX re-expression in *Enpp2*-knockdown tumors decreased eosinophil numbers back to baseline levels. Moreover, ATX depletion led to activation of tumor-associated eosinophils, as evidenced by their degranulation and disrupted membrane architecture. Thus, the presence of eosinophils within the PDAC microenvironment is associated with reduced tumor burden.

Next, the authors performed eosinophil depletion experiments. As expected, eosinophil deficiency led to increased tumor burden, albeit to a modest degree. In the ATX-deficient setting, eosinophil depletion restored tumor growth to control levels, consistent with ATX/LPA promoting tumor progression by repelling infiltrating eosinophils. Interestingly, eosinophil-depleted PDAC tumors showed a significant decrease in $CD8^+$ T cell abundance. Although the functional state of these $CD8^+$ T cells was not determined, it is of note that eosinophils display intricate crosstalk with T cells and can enhance $CD8^+$ T cell activation to improve immunotherapy outcome in patients with breast cancer [9].

Eosinophils are attracted to inflamed tissues by eotaxins, which bind to chemokine receptor CCR3 [7]. Expression of CCL11 (eotaxin-1) was uniquely and strongly upregulated in human PDAC

cells treated with ATX inhibitors [6]. Consistently, CCL11 expression and secretion were upregulated in ATX-deficient PDAC cells, both *in vitro* and *in vivo*. Enforced *Ccl11* overexpression in PDAC cells increased eosinophil infiltration into the TME. This was sufficient to reduce tumor burden and phenocopy ATX deficiency. As a further test, antagonizing CCR3 in tumor-bearing mice rescued tumor growth and reduced eosinophil accumulation in the ATX-depleted tumor setting, at least in part.

This finding raises the key question of how ATX acts to suppress CCL11 production in PDAC cells. The authors focused on the AP-1/c-Jun transcription factor, a regulator of CCL11 expression in other cellular contexts. Phosphorylation and nuclear trafficking of c-Jun were both increased in ATX-deficient PDAC cells, as were phospho-c-Jun levels in PDAC tumors. Whereas AP-1/c-Jun is usually activated upon receptor stimulation, its negative regulation suggests involvement of an inhibitory LPA receptor. PDAC cells express LPAR1, LPAR2, and LPAR6. But since antagonists of LPAR1 and LPAR2 had no effect on *Ccl11* transcription [6], $G\alpha_{13}$-coupled LPAR6 qualifies as the inhibitory receptor. The putative LPAR6-$G\alpha_{13}$-linked signaling pathway that downregulates *Ccl11* expression has yet to be deciphered, particularly in the context of LPAR1- and KRAS-driven signaling cascades in PDAC cells.

In conclusion, the study by Bhattacharyya *et al.* indicates that PDAC cell-derived ATX closes the door on eosinophils by limiting their CCL11-driven tumor infiltration to facilitate PDAC progression. It does so via an as yet unknown LPAR signaling pathway that downregulates c-Jun-dependent CCL11 expression in PDAC cells, as schematically illustrated in Figure 1. The study thus reveals a new ATX-mediated immune escape mechanism and highlights the antitumor potential of eosinophils in PDAC [6]. It remains to be investigated whether eosinophils kill PDAC tumor cells in a direct manner or by engaging cytotoxic $CD8^+$ T cells, a scenario that has recently come to light [9].

Future studies should now explore ATX-mediated eosinophil exclusion in other tumor models and how it may integrate with $CD8^+$ T cell silencing. In this respect, it remains to be elucidated why tumor-infiltrating $CD8^+$ T cells fail to respond to ATX ablation in the PDAC model [6], as it is at variance with previous findings

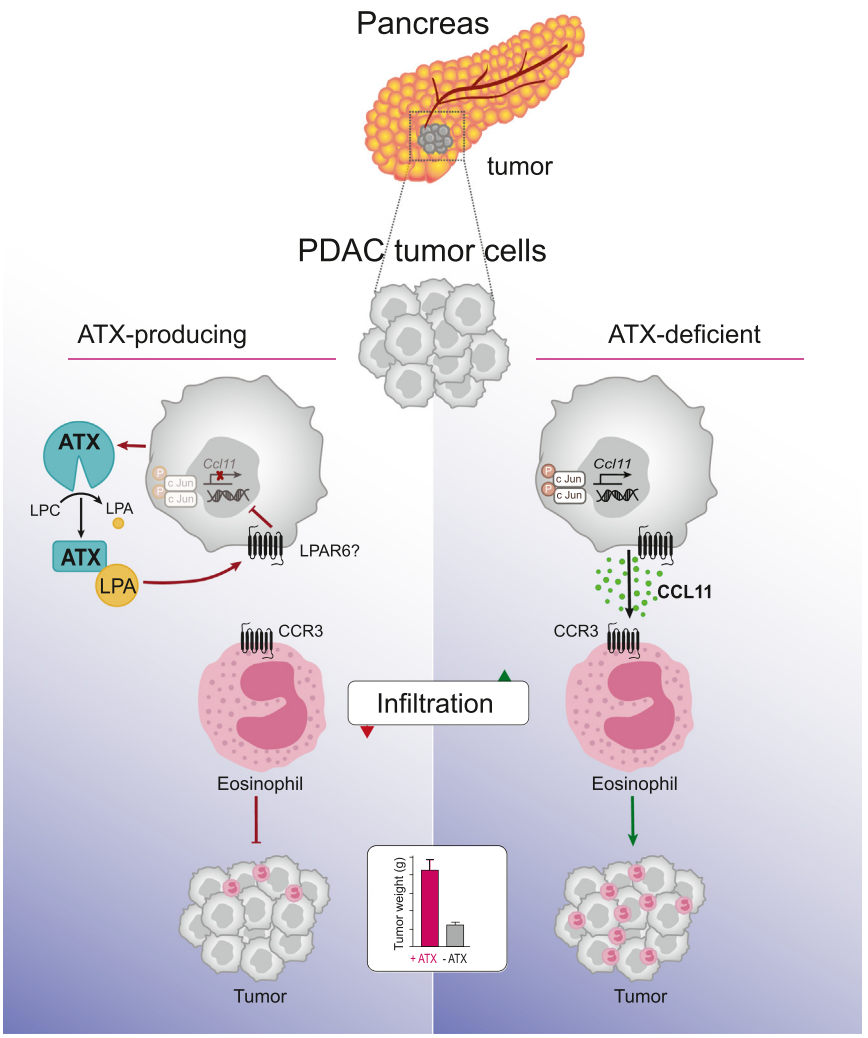

Figure 1. ATX/LPA signaling suppresses a CCL11–eosinophil axis to promote pancreatic ductal adenocarcinoma (PDAC) progression. Simplified scheme illustrating how ATX/LPA disrupts CCL11-CCR3-mediated infiltration of eosinophils into the pancreatic tumor microenvironment to suppress tumor cell killing. PDAC cell-derived ATX downregulates AP-1/c-Jun-dependent *Ccl11* transcription and subsequent CCL11 secretion in an autocrine feedback loop, which is not observed in the ATX-deficient setting. The putative LPAR6 route that inhibits CCL11 production has yet to be delineated. Thus, ATX/LPA promotes PDAC progression by enhancing tumor cell proliferation (not depicted), while suppressing eosinophil infiltration. Abbreviations: ATX, autotaxin; C-C motif chemokine 11; CCL11 (eotaxin-1), CCR3, C-C motif chemokine receptor 3; LPA, lysophosphatidic acid; LPAR6, LPA receptor 6; LPC, lysophosphatidylcholine.

[2,4,5]. Does it reflect a unique feature of the highly immunosuppressive PDAC microenvironment or a limitation of the tumor models used? The use of more advanced PDAC models may help solve this issue. Furthermore, the authors show that eosinophils express multiple LPA receptors [6]. Could LPA serve as a chemorepellent for eosinophils, as it does for $CD8^+$ T cells [2,4,5], and oppose chemotactic CCL11 activity? Although there does not seem to be a need to invoke an eosinophil-repelling role for ATX/LPA for now, it will be important to determine how ATX/LPA may affect the functionality of eosinophils *in vitro*.

Lastly, and more generally, future studies should take stroma-secreted ATX into account as this ATX pool can be quite substantial and may impact immune regulation differently from tumor cell-secreted ATX, depending on the spatial location of secreted ATX and its diffusion rate within the TME.

Regardless of these unknowns, the antitumor benefits of ATX inhibition in PDAC and beyond should be further assessed in combination with immune checkpoint blockade and by co-targeting potent immunosuppressive cytokines such as TGFβ, an approach that has recently been initiated [10]. A new ATX inhibitor is currently being evaluated in clinical trials in PDAC patients (NCT05586516). Based on the new findings, it would be relevant to monitor the dynamics and functional states of tumor-associated eosinophil in these patients.

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Declaration of interests

W.H.M. contributed to the discovery of IOA-289 and has received consultancy fees from iOnctura SA. E.M-R. has no conflicts to declare.

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