IN THE SPOTLIGHT

Adipocytes and Neutrophils Give a Helping Hand to Pancreatic Cancers

Vincenzo Bronte1 and Giampaolo Tortora2

Summary: Obesity-induced inflammation can build up a confined microenvironment in pancreatic adenocarcinoma that is associated with increased desmoplasia, neutrophil recruitment, reduced delivery of chemotherapeutic drugs, and immune evasion. Targeting molecular pathways empowering this circuit might represent a necessary measure to reach clinical efficacy for combination therapies in patients with excess body weight.

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See related article by Incio et al., p. 852 (3).

Excess body weight amplifies the relative mortality risk in patients with pancreatic ductal adenocarcinoma (PDAC), a tumor characterized by a desmoplastic fibrotic reaction due to enhanced extracellular matrix deposition by activated pancreatic stellate cells (PSC). Moreover, pancreatic steatosis is associated with heightened PDAC risk and plays a negative prognostic role in patients with PDAC (1, 2). Starting from previously published data showing that obesity increases the proinflammatory cytokine IL1β and fuels an inflammatory milieu associated with accelerated tumor growth and metastasis formation, Incio and colleagues show that obesity shapes a distinctive PDAC microenvironment characterized by adipocyte accumulation and hypertrophy, local cross-talk between tumor-associated neutrophils (TAN) and PSCs, and the production of proinflammatory and profibrotic factors, which in turn favor tumor progression and severely limit the delivery of chemotherapeutic drugs (3). Some crucial molecular events support the intricate cell network that is established by diet-induced obesity. In invading the neighboring visceral white adipose tissue, whose adipocytes abundantly express the angiotensin II type-1 receptor (AT1), PDAC becomes enriched in enlarged adipocytes, collagen, and activated αSMA+ PSCs. This heightened desmoplastic context negatively affects blood perfusion and both delivery and therapeutic efficacy of the chemotherapeutic drug 5-Fluorouracil, one of the drugs commonly used in patients affected by PDAC. Such failure was reverted to that observed in lean mice by treatment with the FDA-approved AT1 inhibitor losartan or by AT1 genetic ablation (Agr1α−/− mice; ref. 3). Obesity promoted TAN recruitment in PDAC, which in turn activated PSCs and limited vascular perfusion. Adipocytes and PSCs expressed high levels of IL1β that mediated the obesity-dependent TAN recruitment. Neutrophil depletion, IL1β inhibition, and AT1 blockade also increased CD8+ T cells and reduced T regulatory lymphocytes in tumors from obese but not lean mice, suggesting a role for TANs in regulating the immune contexture of PDAC. In line with the preclinical data, a study in 309 patients with PDAC confirmed that adjuvant chemotherapy following surgical resection resulted in a better overall survival in normal-weight patients compared with obese patients (3).

These data establish an important link between AT1+ adipocytes, IL1 production, neutrophil activation, and desmoplasia in pancreatic cancer (Fig. 1). IL1 family proteins comprise different cytokines with proinflammatory functions, often integrating endothelial activation and myeloid cell recruitment to optimize pathogen clearance. Among the members, IL1α and IL1β are produced, through different molecular mechanisms, by mesenchymal, epithelial, or myeloid cells but share the same receptor, and their chronic release has been associated with tumor promotion. In response to signals perturbing the mitogenic potential of tissue cells, including oncogenic insults, cells can mount a senescence response leading to a permanent cell-cycle arrest by tumor suppressors, such as p53 and p16INK4a, as well as the secretion of cytokines and proteases, a response termed the senescence-associated secretory phenotype (SASP). Cellular senescence is a potent anticancer mechanism in vitro, but SASP can puzzlingly create a protumorigenic environment in which IL1 plays an essential role. It is possible that this dichotomy is dictated by the interplay between the oncogenic and tissue landscape (Fig. 1), which include the presence and activation state of adipocytes, as supported by the original findings from Incio and colleagues (3). IL1α is produced, together with other inflammatory cytokines, by KRAS-induced senescent cells in mouse models of PDAC through the regulation of the histone-deacetylase-associate protein SIN3B. Genetic ablation of this gene delayed PDAC progression, and the levels of SIN3B in mouse and human PDAC correlated with KRAS-induced production of IL1α (4). Membrane-bound IL1α is the main SASP cytokine regulated by MTOR activation in senescent fibroblasts that can stimulate the growth of prostate cancer cells (5). CD11b+Gr1+ neutrophils recruited in mouse prostate...
tumors of PTEN-null mice, at the onset of senescence, protect proliferating cells and hence support tumor development. These TANs oppose IL1 activity within the tumor by releasing IL1 receptor antagonist, and the beneficial effect of senescence-activating chemotherapy with docetaxel was enhanced by interfering with TAN recruitment (6), further highlighting this loop by independent IL1 cytokine release. Recruited neutrophils establish extensive interactions with other cellular components of the stroma (i.e., adipocytes and PSC), creating a highly fibrotic and poorly vascularized tissue environment that is both refractory to free drug diffusion from blood and hostile to activation of tumor-specific CD8+ T cells. Treg, T regulatory lymphocyte.

**Figure 1.** Cancer cell–intrinsic and –extrinsic cues to inflammation and fibrosis. Proinflammatory IL1 can be produced by either transformed cells or hijacked adipocytes to activate PSC, which can further amplify this loop by independent IL1 cytokine release. Recruited neutrophils establish extensive interactions with other cellular components of the stroma (i.e., adipocytes and PSC), creating a highly fibrotic and poorly vascularized tissue environment that is both refractory to free drug diffusion from blood and hostile to activation of tumor-specific CD8+ T cells. Treg, T regulatory lymphocyte.

with PDAC cells (8). Cancer-intrinsic, oncogene-driven programs can thus variously affect adipocyte/PSC/neutrophil cross-talk, which in turn contributes to tumor development by molding a tumor-promoting stroma landscape (Fig. 1).

The article by Incio and colleagues (3) also touches upon the immune-suppressive environment in PDAC, endorsing the IL1 role already proposed in other cancers. In mouse models of breast cancer dependent on mammary-restricted, combined loss of E-cadherin and p53, neutrophils facilitate metastatic spreading to different organs through a process initiated by tumor-released IL1β and amplified by the IL17 produced by γδ T lymphocytes and a systemic rise in G-CSF cytokine levels. In this cancer model, the tumor-promoting activity of neutrophils was dependent on the inhibitory action they exerted on metastasis-restraining CD8+ T cells (9). Even though IL1β or AT1 blockade resulted in concomitant TAN reduction and CD8+ T-cell increase in PDAC (3), suggesting an immune-suppressive role of obesity-induced neutrophils in limiting adaptive immunity (Fig. 1), a difference with the previous study in breast cancer lies in the observation that neutrophil depletion affected only metastasis formation and not the growth of primary tumor.

As suggested by Incio and colleagues, the different therapeutic options exploited to correct the tumor environment “poisoned” by the adipocyte infiltration in overweight patients might be exploited in combination with immunotherapy strategies reviving tumor-infiltrating CD8+ T cells, like the PD-1/PD-L1 checkpoint inhibitors. From this standpoint, however, it will be necessary to explore in depth the functional and responsive status of tumor-infiltrating CD8+ T cells in lean and obese mice to address whether obesity might either independently induce or aggravate some of the many immune regulatory circuits in cancer based on T-cell exhaustion and/or stroma-associated immune suppression. This is also particularly relevant in consideration of the recent identification of four molecular subtypes of PDAC based on genes recurrently mutated in various signaling pathways (10). Considering the impact of different oncogenes on senescence and production of IL1 cytokine family members, obesity might exert diverse influences in distinctive subgroups of patients with PDAC.

The findings reported by Incio and colleagues (3) open two interesting scenarios, which will require further studies. The first is about the pervasiveness of the “adipocyte poisoning” of the tumor environment, i.e., whether this proinflammatory signature related to obesity can be present in other tumor types and determine specific features of tumor progression, such as fibrosis, immune dysfunction, angiogenesis, and senescence. The second and likely more clinically relevant point is related to the need of individualizing and optimizing combination therapies for obese patients by adding drugs targeting tumor-associated adipocytes.

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No potential conflicts of interest were disclosed.

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REFERENCES


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