Supporting Information

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S1: Detailed interaction between TANs and tumor cells

Lung cancer is still the leading cause of cancer-associated deaths worldwide, with 1.8 million deaths in 2018 [1, 2]. Various cell types such as immune cells, fibroblasts, and endothelial cells in a tumor microenvironment (TME) interact with tumor cells via the cytokines and growth factors. Tumor-associated neutrophils (TANs) are of particular interest because experimental studies showed that they can contribute to the tumor growth, critical invasion, epithelial-mesenchymal transition (EMT), and metastasis of cancer cells [3, 4]. Until recently, neutrophils have been considered as merely a bystander in the TME and metastasis [5–7] but they are emerging as an important player due to consistent and continuous evidences of their tumor-promoting roles [3]. The high neutrophil to lymphocyte ratio (NLR) is considered to be an important indicator of poor prognosis of various cancers [3] including lung cancers [8, 9]. It was shown that cancer cells can secrete CXC chemokines attracting neutrophils to TME [10] and neutrophil invasion is highly correlated with poor clinical outcomes [11, 12]. Neutrophils are the most abundant leukocytes in blood that play important roles in our innate immune system by killing harmful microorganisms via three mechanisms [13]: (i) phagocytosis (engulfing and digestion of bacteria or fungi), (ii) degranulation of cytotoxic enzymes, (iii) neutrophil extracellular traps (NETs), which consist of DNA meshes with cytotoxic enzymes and trap microorganisms in the extracellular space. Therefore, the classical form of neutrophils, called N1 TAN, can induce lysis of tumor cells [14–16] through many mechanisms including reactive oxygen species (ROS)-mediated hypochlorous acid [17, 18] and kill tumor cells via TNF-α [19]. Furthermore, TANs induced from interferons (IFNs) can secrete tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) which then binds to a receptor of tumor cells and passes it to downstream pathways for tumor cell apoptosis [20]. However, tumor-supporting TANs are recruited from tumor cells at a distant TME and infiltrate tumor tissue, leading to tumor growth, invasion, metastasis [21–25] and ultimately, poor clinical outcomes in many cancers [26]. Metastatic cancer cells were able to induce neutrophils to form metastasis-promoting NETs without involving infection processes [27].

While transforming growth factor (TGF-β) is known to facilitate tumor growth, invasion, and metastasis of many types of cancers [28, 29] including breast [30–32] and lung [28] cancers, the tumor-secreted TGF-β was shown to transform N1 TANs (tumor-suppressive phenotype) to N2 TANs (tumor-promoting phenotype) [33–35]. The reverse action of this transformation can be mediated by type I IFN [19, 33], which can inhibit tumor growth [36] through regulation of TYK2, JAK1, STAT family, and their downstream pathways [37].

Excess activity of neutrophil elastase (NE or ELANE) has been shown to cause tissue damage and to harmful remodeling process in lung diseases such as pneumonia, acute lung injury, and cancer [38]. Importantly, NE was shown to infiltrate the TME [39] and promote tumor growth in lung cancers through the PI3K signaling pathways [10]. Neutrophil can also promote the tumor cell invasion by degrading the extracellular matrix (ECM) and basal membrane with NE [40] and matrix metallopeptidase (MMP) [17, 41, 42]. NE was also suggested to induce EMT and metastasis of cancer cells [4, 41, 42]. For example, NE inhibitors were able to inhibit tumor growth and metastasis [40, 43, 44]. TANs were also suggested to drive angiogenesis in malignancy by secreting MMPs, which subsequently promote VEGF secretion [17]. It was shown that neutrophils can promote the tumor cell invasion in the transwell assay [27, 45] and *in vivo* experiments [27, 46, 46].

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