I. Supporting Methods

1. Deterministic description of the intercellular signaling network.

We translated the intercellular signaling network figure 1 into mathematical format by employing population dynamics and Hill functions. The deterministic descriptions are dozens of ordinary differential equations as follows. The meanings of parameters are listed in Supporting Table S1. The computational codes are available upon request, which should be addressed to Y.W.

CELL

(1) LCC

Human lung cancer develops from normal epithelial cells through a multistep process involving successive genetic and epigenetic abnormalities, usually coincident with cigarette smoking [1].

Cigarette smoking, the main risk factor for lung cancer development, causes chronic inflammation, leading to unbalanced cytokine secretion and inflammatory cell recruitment, which favors malignant transformation of epithelial cells [2].

TGF-β inhibits cell proliferation in both SCLC and NSCLC cells and induces apoptosis. Nevertheless, at the later stage of lung cancer tumorigenesis, TGF-β induces angiogenesis, and at this stage, the growth-inhibitory effect of TGF-β is lost by several different mechanisms [1].

During the early phase of epithelial tumorigenesis, TGF-β inhibits primary tumor development and growth by inducing cell cycle arrest and apoptosis. In late stages of tumor progression when tumor cells become resistant to growth inhibition by TGF-β due to inactivation of the TGF-β signaling pathway or aberrant regulation of the cell cycle, the role of TGF-β becomes one of tumor promotion [3].

A subset of NSCLC tumour cells express functional VEGFR2 which can act to promote VEGF-dependent tumour cell growth [4].

M1macrophages recruit other immune cells and engulf tumor cells [2].

In most examined tumors, isolated TAMs are of the immunosuppressive M2 phenotype [2].

The epidermal growth factor receptor (EGFR) and its downstream effector kinases are thought to have important roles in lung cancer cell proliferation [5].

HGF and EGF both induced cell proliferation, and a combination of HGF and EGF had a synergistic effect on cell proliferation in A549(A), H1838 (B), and SKMES (C) [6].

Signaling of FGFs through the FGF receptors (FGFR) has been implicated as an autocrine signaling loop that leads to tumor proliferation and angiogenesis in a variety of NSCLC cell lines [7].

Moreover, FGFR4 can promote NSCLC cell proliferation in vitro [8].

SDF-1 facilitated lung cancer cell proliferation and drug resistance via the CXCR4-mediated signaling passway which involved NF- κ Band Bcl-xL [9].

IL-8 increases cell proliferation in NSCLC cell lines via transactivation of the EGFR and

that this mechanism involves metalloproteinase activity [10].

IGF-1 as one factor produced by alveolar macrophages that directly stimulates neoplastic lung proliferation in vitro [11].

PGE2 promotes NSCLC cell growth through increased α7-nAChR expression [12].

IL10 increased lung cancer cell proliferation in a dose- and time-dependent manner [13].

$$\dot{x}_{LCC} = R_{Epith} p_{LCC\_Epith} + R_{LCC} - d_{LCC}(1+\frac{u_{LCC\_M1} x_{M1}}{s_{M1} + x_{M1}})(\frac{s_{M2}}{s_{M2} + x_{M2}})x_{LCC}$$

$$R_{LCC} = r_{LCC} x_{LCC}(1-\frac{x_{LCC} + x_{CAF} + x_{M1} + x_{M2} + x_{MSC} + x_{Epith}}{x_{\max} A_{angiogenssi}})$$

$$(1+\frac{u_{LCC\_EGF} y_{EGF}^{n_{LCC\_EGF}}}{s_{LCC\_EGF}^{n_{LCC\_EGF}} + y_{EGF}^{n_{LCC\_EGF}}})(1+\frac{u_{LCC\_FGF} y_{FGF}^{n_{LCC\_FGF}}}{s_{LCC\_FGF}^{n_{LCC\_FGF}} + y_{FGF}^{n_{LCC\_FGF}}})(1+\frac{u_{LCC\_HGF} y_{HGF}^{n_{LCC\_HGF}}}{s_{LCC\_HGF}^{n_{LCC\_HGF}} + y_{HGF}^{n_{LCC\_HGF}}})$$

$$(1+\frac{u_{LCC\_IGF-1} y_{IGF-1}^{n_{LCC\_IGF-1}}}{s_{LCC\_IGF-1}^{n_{LCC\_IGF-1}} + y_{IGF-1}^{n_{LCC\_IGF-1}}})(1+\frac{u_{LCC\_IL-10} y_{IL-10}^{n_{LCC\_IL-10}}}{s_{LCC\_IL-10}^{n_{LCC\_IL-10}} + y_{IL-10}^{n_{LCC\_IL-10}}})(1+\frac{u_{LCC\_VEGF} y_{VEGF}^{n_{LCC\_VEGF}}}{s_{LCC\_VEGF}^{n_{LCC\_VEGF}} + y_{VEGF}^{n_{LCC\_VEGF}}})$$

$$(1+\frac{u_{LCC\_SDF-1} y_{SDF-1}^{n_{LCC\_SDF-1}}}{s_{LCC\_SDF-1}^{n_{LCC\_SDF-1}} + y_{SDF-1}^{n_{LCC\_SDF-1}}})(1+\frac{u_{LCC\_PGE2} y_{PGE2}^{n_{LCC\_PGE2}}}{s_{LCC\_PGE2}^{n_{LCC\_PGE2}} + y_{PGE2}^{n_{LCC\_PGE2}}})$$

$$R_{Epith} = r_{Epith} x_{Epith}(1-\frac{x_{LCC} + x_{CAF} + x_{M1} + x_{M2} + x_{MSC} + x_{Epith}}{x_{\max} A_{angiogenssi}})(1+\frac{u_{Epith\_IL-8} y_{Epith\_IL-8}^{n_{Epith\_IL-8}}}{s_{Epith\_IL-8}^{n_{Epith\_IL-8}} + y_{Epith\_IL-8}^{n_{Epith\_IL-8}}})$$

$$(1+\frac{u_{Epith\_EGF} y_{Epith\_EGF}^{n_{Epith\_EGF}}}{s_{Epith\_EGF}^{n_{Epith\_EGF}} + y_{Epith\_EGF}^{n_{Epith\_EGF}}})$$

$$A_{angiogenesis} = (1+\frac{u_{cell\_VEGF} y_{VEGF}^{n_{cell\_VEGF}}}{s_{cell\_VEGF}^{n_{cell\_VEGF}} + y_{VEGF}^{n_{cell\_VEGF}}})(1+\frac{u_{cell\_PDGF} y_{PDGF}^{n_{cell\_PDGF}}}{s_{cell\_PDGF}^{n_{cell\_PDGF}} + y_{PDGF}^{n_{cell\_PDGF}}})(1+\frac{u_{cell\_FGF} y_{FGF}^{n_{cell\_FGF}}}{s_{cell\_FGF}^{n_{cell\_FGF}} + y_{FGF}^{n_{cell\_FGF}}})$$

$$(1+\frac{u_{cell\_IL6} y_{IL6}^{n_{cell\_IL6}}}{s_{cell\_IL6}^{n_{cell\_IL6}} + y_{IL6}^{n_{cell\_IL6}}})(1+\frac{u_{cell\_IL8} y_{IL8}^{n_{cell\_IL8}}}{s_{cell\_IL8}^{n_{cell\_IL8}} + y_{IL8}^{n_{cell\_IL8}}})(1+\frac{u_{cell\_SDF1} y_{SDF1}^{n_{cell\_SDF1}}}{s_{cell\_SDF1}^{n_{cell\_SDF1}} + y_{SDF1}^{n_{cell\_SDF1}}})$$

$$(1+\frac{u_{cell\_MCP1} y_{MCP1}^{n_{cell\_MCP1}}}{s_{cell\_MCP1}^{n_{cell\_MCP1}} + y_{MCP1}^{n_{cell\_MCP1}}})(1+\frac{u_{cell\_TGFb} y_{TGFb}^{n_{cell\_TGFb}}}{s_{cell\_TGFb}^{n_{cell\_TGFb}} + y_{TGFb}^{n_{cell\_TGFb}}})(1+\frac{u_{cell\_TNF-\alpha} y_{TNF-\alpha}^{n_{cell\_TNF-\alpha}}}{s_{cell\_TNF-\alpha}^{n_{cell\_TNF-\alpha}} + y_{TNF-\alpha}^{n_{cell\_TNF-\alpha}}})$$

(2) CAF

Local fibroblasts or fibroblast precursors, stimulated by members of the PDGF or TGF-β family, have generally been considered as the major source of CAFs [14].

There is growing evidence that the origins of CAFs in lung cancer arise directly from reprogramming of resident fibroblasts [15].

TGF-β, platelet-derived growth factor (PDGF) and fibroblast growth factor 2 (FGF2), all of which are key mediators of fibroblast activation and tissue fibrosis [16].

MSCs are thought to act as precursors for cancer-associated fibroblasts (CAFs) [17].

PDGF-B-aFBs induced differentiation of MSCs into myofibroblast [18].

TGF-β participates in the process of differentiation from MSCs to CAFs, and coordinates the increase of α-SMA and the decrease of gelsolin to promote MSC differentiation [19].

TGF-β has been recognized as the most potent inducer of transformation of fibroblasts to CAFs [20].

Paracrine stimulation by PDGFs secreted from cancer cells has been shown to induce CAFs in tumor stroma to recruit and proliferate in in vivo transplant tumor models of melanoma, breast carcinoma, colorectal carcinoma, and lung carcinoma [21].

In vitro assays indicated that PGE2 increased CAF proliferation and migration [22].

$$\dot{x}_{CAF} = c_{CAF\_TGF-\beta}\left(\frac{y_{TGF-\beta}^{n_{CAF\_TGF-\beta}}}{s_{CAF\_TGF-\beta}^{n_{CAF\_TGF-\beta}} + y_{TGF-\beta}^{n_{CAF\_TGF-\beta}}}\right) + c_{CAF\_PDGF}\left(\frac{y_{PDGF}^{n_{CAF\_PDGF\_r}}}{s_{CAF\_PDGF\_r}^{n_{CAF\_PDGF\_r}} + y_{PDGF}^{n_{CAF\_PDGF\_r}}}\right) +$$

$$c_{CAF\_FGF}\left(\frac{y_{FGF}^{n_{CAF\_FGF}}}{s_{CAF\_FGF}^{n_{CAF\_FGF}} + y_{FGF}^{n_{CAF\_FGF}}}\right) + R_{MSC}\, p_{CAF\_MSC}\left(1 + \frac{u_{CAF\_MSC\_PDGF}\, y_{PDGF}^{n_{CAF\_MSC\_PDGF}}}{s_{CAF\_MSC\_PDGF}^{n_{CAF\_MSC\_PDGF}} + y_{PDGF}^{n_{CAF\_MSC\_PDGF}}}\right)$$

$$\left(1 + \frac{u_{CAF\_MSC\_TGF-\beta}\, y_{TGF-\beta}^{n_{CAF\_MSC\_TGF-\beta}}}{s_{CAF\_MSC\_TGF-\beta}^{n_{CAF\_MSC\_TGF-\beta}} + y_{TGF-\beta}^{n_{CAF\_MSC\_TGF-\beta}}}\right) + \mathrm{R}_{CAF}\left(1 - p_{MSC\_CAF}\left(\frac{s_{MSC\_CAF\_PDGF}^{n_{MSC\_CAF\_PDGF}}}{s_{MSC\_CAF\_PDGF}^{n_{MSC\_CAF\_PDGF}} + y_{PDGF}^{n_{MSC\_CAF\_PDGF}}}\right)\right.\right.$$

$$\left.\left.\left(\frac{s_{MSC\_CAF\_TGF-\beta}^{n_{MSC\_CAF\_TGF-\beta}}}{s_{MSC\_CAF\_TGF-\beta}^{n_{MSC\_CAF\_TGF-\beta}} + y_{TGF-\beta}^{n_{MSC\_CAF\_TGF-\beta}}}\right)\right)\right) - d_{CAF}\, x_{CAF}$$

$$R_{CAF} = r_{CAF}\, x_{CAF}\left(1 - \frac{x_{LCC} + x_{CAF} + x_{M1} + x_{M2} + x_{MSC} + x_{Epith}}{x_{\max} A_{angiogensi}}\right)\left(1 + \frac{u_{CAF\_PDGF\_p}\, y_{PDGF}^{n_{CAF\_PDGF\_p}}}{s_{CAF\_PDGF\_p}^{n_{CAF\_PDGF\_p}} + y_{PDGF}^{n_{CAF\_PDGF\_p}}}\right)$$

$$\left(1 + \frac{u_{CAF\_PGE2}\, y_{PGE2}^{n_{CAF\_PGE2}}}{s_{CAF\_PGE2}^{n_{CAF\_PGE2}} + y_{PGE2}^{n_{CAF\_PGE2}}}\right)$$

$$R_{MSC} = r_{MSC}\, x_{MSC}\left(1 - \frac{x_{LCC} + x_{CAF} + x_{M1} + x_{M2} + x_{MSC} + x_{Epith}}{x_{\max} A_{angiogensi}}\right)$$

(3) M1

The production of chemotactic factors such as CCL2, VEGF and M-CSF in the tumor microenvironment recruits macrophages [23].

Other chemokines involved in monocyte recruitment are CCL5, CCL7, CXCL8, and CXCL12, as well as cytokines such as VEGF, PDGF and the growth factor M-CSF [24].

Although the organ-specific interplay between TRMs and MDMs is still being elucidated, recent cell tracking studies argue that, in most cases, the majority of TAMs are derived from blood monocytes, recruited to tumors via the CCL2 chemokine [25].

Monocyte/macrophage homing to the tumor site in response to several immunomodulatory factors secreted by tumor cells, such as MCP-1 [2].

IFN-γ, lipopolysaccharides, TNF-α, and GM-CSF induce monocytes to differentiate into M1 macrophages that express high levels of inducible nitric oxide synthase (iNOS), TNF-α,

IL-1β, IL-6, IL-12, IL-18, IL-23, CXCL10, human leukocyte antigen DR, and reactive oxygen and nitrogen intermediates [26].

Cultured lung AC cells produce several macrophage chemoattractants, including IL-1β and GM-CSF [11].

Lung tumor cells over-expressing IL-1β enhanced macrophage recruitment and tumor angiogenesis when implanted into syngeneic mice [11].

CAFs, for example, secrete MCP-1 (CCL2), IL-6 and TNF-α, driving M1 to the M2 phenotype [2].

$$\dot{x}_{M1} = [c_M(1+(\frac{u_{M\_MCP-1}y_{MCP-1}^{n_{M\_MCP-1}}}{s_{M\_MCP-1}^{n_{M-MCP-1}}+y_{MCP-1}^{n_{M\_MCP-1}}})+(\frac{u_{M\_VEGF}y_{VEGF}^{n_{M\_VEGF}}}{s_{M\_VEGF}^{n_{M\_VEGF}}+y_{VEGF}^{n_{M\_VEGF}}})+(\frac{u_{M\_PDGF}y_{PDGF}^{n_{M\_PDGF}}}{s_{M\_PDGF}^{n_{M\_PDGF}}+y_{PDGF}^{n_{M\_PDGF}}})+(\frac{u_{M\_M-CSF}y_{M-CSF}^{n_{M\_M-CSF}}}{s_{M\_M-CSF}^{n_{M\_M-CSF}}+y_{M-CSF}^{n_{M\_M-CSF}}})]$$

$$[\frac{(u_{M1\_M\_IFN-\gamma}y_{IFN-\gamma}+u_{M1\_M\_TNF-\alpha}y_{TNF-\alpha}+u_{M1\_M\_GM-CSF}y_{GM-CSF})}{(u_{M1\_M\_IFN-\gamma}y_{IFN-\gamma}+u_{M1\_M\_TNF-\alpha}y_{TNF-\alpha}+u_{M1\_M\_GM-CSF}y_{GM-CSF})+(u_{M2\_M\_IL-10}y_{IL-10}+u_{M2\_M\_PGE2}y_{PGE2})}]$$

$$+x_{M2}p_{M1\_M2}[(\frac{u_{M1\_M2\_IFN-\gamma}y_{IFN-\gamma}^{n_{M1\_M2\_IFN-\gamma}}}{s_{M1\_M2\_IFN-\gamma}^{n_{M1\_M2\_IFN-\gamma}}+y_{IFN-\gamma}^{n_{M1\_M2\_IFN-\gamma}}}+\frac{u_{M1\_M2\_TNF-\alpha}y_{TNF-\alpha}^{n_{M1\_M2\_TNF-\alpha}}}{s_{M1\_M2\_TNF-\alpha}^{n_{M1\_M2\_TNF-\alpha}}+y_{TNF-\alpha}^{n_{M1\_M2\_TNF-\alpha}}}$$

$$+u_{M1\_M2}(\frac{y_{IFN-\gamma}^{n_{M1\_M2\_IFN-\gamma}}}{s_{M1\_M2\_IFN-\gamma}^{n_{M1\_M2\_IFN-\gamma}}+y_{IFN-\gamma}^{n_{M1\_M2\_IFN-\gamma}}}\frac{y_{TNF-\alpha}^{n_{M1\_M2\_TNF-\alpha}}}{s_{M1\_M2\_TNF-\alpha}^{n_{M1\_M2\_TNF-\alpha}}+y_{TNF-\alpha}^{n_{M1\_M2\_TNF-\alpha}}})](\frac{s_{M1\_M2\_IL-10}^{n_{M1\_M2\_IL-10}}}{s_{M1\_M2\_IL-10}^{n_{M1\_M2\_IL-10}}+y_{IL-10}^{n_{M1\_M2\_IL-10}}})$$

$$-d_{M1}x_{M1}$$

(4) M2

The production of chemotactic factors such as CCL2, VEGF and M-CSF in the tumor microenvironment recruits macrophages [23].

Other chemokines involved in monocyte recruitment are CCL5, CCL7, CXCL8, and CXCL12, as well as cytokines such as VEGF, PDGF and the growth factor M-CSF [24].

Although the organ-specific interplay between TRMs and MDMs is still being elucidated, recent cell tracking studies argue that, in most cases, the majority of TAMs are derived from blood monocytes, recruited to tumors via the CCL2 chemokine [25].

MSCs contribute to cancer progression by producing chemokines which, via CCR2, recruit TAMs [17].

Monocytes/macrophages are homing to the tumor site in response to several immunomodulatory factors secreted by tumor cells, such as MCP-1 [2].

CAFs, for example, secrete MCP-1 (CCL2), IL-6 and TNF-α, driving M1 to the M2 phenotype [2].

IL-4, IL-10, IL-13, IL-21, activin A, immune complexes, and glucocorticoids are able to induce monocyte differentiation into M2 macrophages that express high levels of arginase (ARG)-1, IL-1RA, IL-10, CCL22, mannose receptor, galactose receptor, and CD163 antigen [26].

PGE2 facilitates M2 macrophage differentiation [26].

$$\dot{x}_{M2} = [c_M(1+(\frac{u_{M\_MCP-1} y_{MCP-1}^{n_{M\_MCP-1}}}{s_{MCP-1}^{n_{M-MCP-1}} + y_{MCP-1}^{n_{M\_MCP-1}}}) + (\frac{u_{M\_VEGF} y_{VEGF}^{n_{M\_VEGF}}}{s_{M\_VEGF}^{n_{M\_VEGF}} + y_{VEGF}^{n_{M\_VEGF}}}) + (\frac{u_{M\_PDGF} y_{PDGF}^{n_{M\_PDGF}}}{s_{M\_PDGF}^{n_{M\_PDGF}} + y_{PDGF}^{n_{M\_PDGF}}}) + (\frac{u_{M\_M-CSF} y_{M-CSF}^{n_{M\_M-CSF}}}{s_{M\_M-CSF}^{n_{M\_M-CSF}} + y_{M-CSF}^{n_{M\_M-CSF}}})]$$

$$[\frac{(u_{M2\_M\_IL-10} y_{IL-10} + u_{M2\_M\_PGE2} y_{PGE2})}{(u_{M1\_M\_IFN-\gamma} y_{IFN-\gamma} + u_{M1\_M\_TNF-\alpha} y_{TNF-\alpha} + u_{M1\_M\_GM-CSF} y_{GM-CSF}) + (u_{M2\_M\_IL-10} y_{IL-10} + u_{M2\_M\_PGE2} y_{PGE2})}]$$

$$- x_{M2} p_{M1\_M2} [(\frac{u_{M1\_M2\_IFN-\gamma} y_{IFN-\gamma}^{n_{M1\_M2\_IFN-\gamma}}}{s_{M1\_M2\_IFN-\gamma}^{n_{M1\_M2\_IFN-\gamma}} + y_{IFN-\gamma}^{n_{M1\_M2\_IFN-\gamma}}} + \frac{u_{M1\_M2\_TNF-\alpha} y_{TNF-\alpha}^{n_{M1\_M2\_TNF-\alpha}}}{s_{M1\_M2\_TNF-\alpha}^{n_{M1\_M2\_TNF-\alpha}} + y_{TNF-\alpha}^{n_{M1\_M2\_TNF-\alpha}}}$$

$$+ u_{M1\_M2} (\frac{y_{IFN-\gamma}^{n_{M1\_M2\_IFN-\gamma}}}{s_{M1\_M2\_IFN-\gamma}^{n_{M1\_M2\_IFN-\gamma}} + y_{IFN-\gamma}^{n_{M1\_M2\_IFN-\gamma}}} \frac{y_{TNF-\alpha}^{n_{M1\_M2\_TNF-\alpha}}}{s_{M1\_M2\_TNF-\alpha}^{n_{M1\_M2\_TNF-\alpha}} + y_{TNF-\alpha}^{n_{M1\_M2\_TNF-\alpha}}})](\frac{s_{M1\_M2\_IL-10}^{n_{M1\_M2\_IL-10}}}{s_{M1\_M2\_IL-10}^{n_{M1\_M2\_IL-10}} + y_{IL-10}^{n_{M1\_M2\_IL-10}}})$$

$$- d_{M2} x_{M2}$$

(5) MSC

MCP-1/CCR2 axis took an important role in HUMSCs' homing to lung cancer [27].

Release of chemoattractant molecules from the tumor and expression of the corresponding receptors in MSCs is necessary for homing of MSCs to the tumor site. Some of these cytokine/receptor pairs are SDF-1/CXCR4, SCF/c-Kit, HGF/c-Met, VEGF/VEGFR, monocyte chemotactic protein (MCP)/CCR2 and HMGB1/RAGE [2].

PDGF induced differentiation of MSCs into myofibroblast [18].

TGF-β participates in the process of differentiation from MSCs to CAFs, and coordinates the increase of α-SMA and the decrease of gelsolin to promote MSC differentiation [19].

$$\dot{x}_{MSC} = c_{MSC\_MCP-1}(\frac{y_{MCP-1}^{n_{MSC\_MCP-1}}}{s_{MSC\_MCP-1}^{n_{MSC\_MCP-1}} + y_{MCP-1}^{n_{MSC\_MCP-1}}}) + c_{MSC\_SDF-1}(\frac{y_{SDF-1}^{n_{MSC\_SDF-1}}}{s_{MSC\_SDF-1}^{n_{MSC\_SDF-1}} + y_{SDF-1}^{n_{MSC\_SDF-1}}}) + c_{MSC\_HGF}(\frac{y_{HGF}^{n_{MSC\_HGF}}}{s_{MSC\_HGF}^{n_{MSC\_HGF}} + y_{HGF}^{n_{MSC\_HGF}}})$$

$$c_{MSC\_VEGF}(\frac{y_{VEGF}^{n_{MSC\_VEGF}}}{s_{MSC\_VEGF}^{n_{MSC\_VEGF}} + y_{VEGF}^{n_{MSC\_VEGF}}}) + R_{MSC}(1 - p_{CAF\_MSC}(1 + \frac{u_{CAF\_MSC\_PDGF} y_{PDGF}^{n_{CAF\_MSC\_PDGF}}}{s_{CAF\_MSC\_PDGF}^{n_{CAF\_MSC\_PDGF}} + y_{PDGF}^{n_{CAF\_MSC\_PDGF}}})$$

$$(1 + \frac{u_{CAF\_MSC\_TGF-\beta} y_{TGF-\beta}^{n_{CAF\_MSC\_TGF-\beta}}}{s_{CAF\_MSC\_TGF-\beta}^{n_{CAF\_MSC\_TGF-\beta}} + y_{TGF-\beta}^{n_{CAF\_MSC\_TGF-\beta}}})) + R_{CAF} p_{MSC\_CAF} (\frac{s_{MSC\_CAF\_PDGF}^{n_{MSC\_CAF\_PDGF}}}{s_{MSC\_CAF\_PDGF}^{n_{MSC\_CAF\_PDGF}} + y_{PDGF}^{n_{MSC\_CAF\_PDGF}}})$$

$$(\frac{s_{MSC\_CAF\_TGF-\beta}^{n_{MSC\_CAF\_TGF-\beta}}}{s_{MSC\_CAF\_TGF-\beta}^{n_{MSC\_CAF\_TGF-\beta}} + y_{TGF-\beta}^{n_{MSC\_CAF\_TGF-\beta}}}) - d_{MSC}x_{MSC}$$

(6) Epith

Various in vitro studies have demonstrated an effect of IL-8 on epithelial cell proliferation [10].

EGF increase epithelial proliferation [10].

$$\dot{x}_{Epith} = R_{Epith}(1 - p_{LCC\_Epith}) - d_{Epith}x_{Epith}$$

CYTOKINE

(1) IL-1β

Cultured lung AC cells produce several macrophage chemoattractants, including IL-1β and GM-CSF [11].

M1 macrophages that express high levels of inducible nitric oxide synthase (iNOS), TNF-α, IL-1β, IL-6, IL-12, IL-18, IL-23, CXCL10, human leukocyte antigen DR, and reactive oxygen and nitrogen intermediates [26].

$$\dot{y}_{IL-1\beta} = k_{IL-1\beta\_LCC}x_{LCC} + k_{IL-1\beta\_M1}x_{M1} - d_{IL-1\beta}y_{IL-1\beta}$$

(2) IL-6

M1 macrophages exert proinflammatory responses by secreting cytokines such as IL-1, IL-6 [2].

MSCs express several angiogenic factors, such as VEGF, angiopoietin-1, PDGF, FGF-2, FGF-6, IL-6 and IL-8 [2].

CAFs secrete MCP-1 (CCL2), IL-6 and TNF-α, driving M1 to the M2 phenotype [2].

Bronchial epithelial cells can express mRNA for IL-8, IL-6 and GM-CSF and secrete the corresponding proteins, and that both phenomena can be enhanced by cytokines such as IL-1β [28].

$$\dot{y}_{IL-6} = k_{IL-6\_MSC}x_{MSC} + k_{IL-6\_M1}x_{M1} + k_{IL-6\_CAF}x_{CAF} + k_{IL-6\_Epith}x_{Epith}(1 + \frac{u_{IL-6\_IL-1\beta}y_{IL-1\beta}^{n_{IL-6\_IL-1\beta}}}{s_{IL-6\_IL-1\beta}^{n_{IL-6\_IL-1\beta}} + y_{IL-1\beta}^{n_{IL-6\_IL-1\beta}}})$$

$$- d_{IL-6}y_{IL-6}$$

(3) IL-8

MSCs express several angiogenic factors, such as VEGF, angiopoietin-1, PDGF, FGF-2, FGF-6, IL-6 and IL-8 [2].

Enhancement of tumor angiogenesis by CAFs can be mediated either directly, by

secreting pro-angiogenic factors including IL-8/CXCL8, vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF)-2 [29].

NSCLC cells produced significant amounts of IL-8 [30].

IL-1β induces IL-8 released by A549 and normal human bronchial epithelial (NHBE) cells [31].

$$\dot{y}_{IL-8} = k_{IL-8\_MSC}x_{MSC} + k_{IL-8\_CAF}x_{CAF} + k_{IL-8\_LCC}x_{LCC}(1+\frac{u_{IL-8\_IL-1\beta\_LCC}y_{IL-1\beta}^{n_{IL-8\_IL-1\beta\_LCC}}}{s_{IL-8\_IL-1\beta\_LCC}^{n_{IL-8\_IL-1\beta\_LCC}} + y_{IL-1\beta}^{n_{IL-8\_IL-1\beta\_LCC}}})$$

$$+ k_{IL-8\_Epith}x_{Epith}(1+\frac{u_{IL-8\_IL-1\beta\_Epith}y_{IL-1\beta}^{n_{IL-8\_IL-1\beta\_Epith}}}{s_{IL-8\_IL-1\beta\_Epith}^{n_{IL-8\_IL-1\beta\_Epith}} + y_{IL-1\beta}^{n_{IL-8\_IL-1\beta\_Epith}}}) - d_{IL-8}y_{IL-8}$$

(4) IL-10

M2 macrophages that express high levels of arginase (ARG)-1, IL-1RA, IL-10, CCL22, mannose receptor, galactose receptor, and CD163 antigen [26].

In the EGF-treated lung cancer cells, IL10 secretion was also increased [13].

$$\dot{y}_{IL-10} = k_{IL-10\_M2}x_{M2}(\frac{s_{IL-10\_IL-10}^{n_{IL-10\_IL-10}}}{s_{IL-10\_IL-10}^{n_{IL-10\_IL-10}} + y_{IL-10\_IL-10}^{n_{IL-10\_IL-10}}}) + k_{IL-10\_LCC}x_{LCC}(1+\frac{u_{IL-10\_EGF}y_{EGF}^{n_{IL-10\_EGF}}}{s_{IL-10\_EGF}^{n_{IL-10\_EGF}} + y_{EGF}^{n_{IL-10\_EGF}}}) - d_{IL-10}y_{IL-10}$$

(5) VEGF

Lung cancers frequently produce high levels of VEGF [1].

MSCs express several angiogenic factors, such as VEGF, angiopoietin-1, PDGF, FGF-2, FGF-6, IL-6 and IL-8 [2].

Enhancement of tumor angiogenesis by CAFs can be mediated either directly, by secreting pro-angiogenic factors including interleukin (IL)-8/CXCL8, vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF)-2 [29].

TGF-β induces the expression of VEGF mRNA and protein in AKR-2B mouse embryo fibroblasts and A549cells [32].

Hypoxia increased VEGF protein levels in medium ofA549 cells, 1HAEo2-1HAEo2 bronchial cells, and Human bronchial epithelial cells (HBECs) [33].

TGF-β1 induced and hypoxia induced VEGF expression by human lung epithelial cells may promote neovascularization [33].

The secretion of VEGF and MIP-2 from LLC/IL-1β cells was further induced by HGF [34].

$$\dot{y}_{VEGF} = k_{VEGF\_LCC}x_{LCC}(1+\frac{u_{VEGF\_TGF-\beta\_LCC}y_{TGF-\beta}^{n_{VEGF\_TGF-\beta\_LCC}}}{s_{VEGF\_TGF-\beta\_LCC}^{n_{VEGF\_TGF-\beta\_LCC}} + y_{TGF-\beta}^{n_{VEGF\_TGF-\beta\_LCC}}})(1+\frac{u_{VEGF\_LCC}x_{LCC}^{n_{VEGF\_LCC}}}{s_{VEGF\_LCC}^{n_{VEGF\_LCC}} + x_{LCC}^{n_{VEGF\_LCC}}})$$

$$(1+\frac{u_{VEGF\_HGF\_LCC}y_{HGF}^{n_{VEGF\_HGF\_LCC}}}{s_{VEGF\_HGF\_LCC}^{n_{VEGF\_HGF\_LCC}} + y_{HGF}^{n_{VEGF\_HGF\_LCC}}}) + k_{VEGF\_Epith}x_{Epith}(1+\frac{u_{VEGF\_TGF-\beta\_Epith}y_{TGF-\beta}^{n_{VEGF\_TGF-\beta\_Epith}}}{s_{VEGF\_TGF-\beta\_Epith}^{n_{VEGF\_TGF-\beta\_Epith}} + y_{TGF-\beta}^{n_{VEGF\_TGF-\beta\_Epith}}})$$

$$+k_{VEGF\_CAF}x_{CAF}(1+\frac{u_{VEGF\_TGF-\beta\_CAF}y_{TGF-\beta}^{n_{VEGF\_TGF-\beta\_CAF}}}{s_{VEGF\_TGF-\beta\_CAF}^{n_{VEGF\_TGF-\beta\_CAF}}+y_{TGF-\beta}^{n_{VEGF\_TGF-\beta\_CAF}}})+k_{VEGF\_M2}x_{M2}+k_{VEGF\_MSC}x_{MSC}-d_{VEGF}y_{VEGF}$$

(6) PDGF

NSCLC cells express the ligand PDGF-B [2].

MSCs express several angiogenic factors, such as VEGF, angiopoietin-1, PDGF,FGF-2, FGF-6,IL-6 and IL-8 [2].

Thrombin induced the secretion and expression of PDGF from bronchial and alveolar epithelial cells [35].

$$\dot{y}_{PDGF}=k_{PDGF\_LCC}x_{LCC}+k_{PDGF\_MSC}x_{MSC}+k_{PDGF\_Epith}x_{Epith}-d_{PDGF}y_{PDGF}$$

(7) EGF

The secretion of EGF and TGF-α by NSCLC cells is necessary to activate EGFR in tumor [36].

M2 macrophages express different proangiogenic cytokines including VEGF, FGF and semaphorin 4D [37].

$$\dot{y}_{EGF}=k_{EGF\_LCC}x_{LCC}+k_{EGF\_M2}x_{M2}-d_{EGF}y_{EGF}$$

(8) FGF

MSCs express several angiogenic factors, such as VEGF, angiopoietin-1, PDGF, FGF-2, FGF-6, IL-6 and IL-8 [2].

The expression of FGF-2 and FGFR-1 was examined in tumor cells and stroma in NSCLC tumors [2].

Enhancement of tumor angiogenesis by CAFs can be mediated either directly, by secreting pro-angiogenic factors including IL-8/CXCL8, vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF)-2 [29].

$$\dot{y}_{FGF}=k_{FGF\_LCC}x_{LCC}+k_{FGF\_MSC}x_{MSC}+k_{FGF\_CAF}x_{CAF}-d_{FGF}y_{FGF}$$

(9) HGF

CAFs secrete potent oncogenic molecules, such as TGF-β and hepatocyte growth factor (HGF) [2].

$$\dot{y}_{HGF}=k_{HGF\_CAF}x_{CAF}-d_{HGF}y_{HGF}$$

(10) IGF-1

Tumor-educated macrophages more than doubled IGF-1 output compared to naïve samples [11].

In mouse lungs, IGF-1 was originally identified as an alveolar macrophage-derived growth factor [11].

$$\dot{y}_{IGF-1} = k_{IGF-1\_M2} x_{M2} + k_{IGF-1\_M1} x_{M1} - d_{IGF-1} y_{IGF-1}$$

(11) PGE2

The autocrine/paracrine role of PGE2 is in up-regulating the expression of CD44 and MMP-2 in human lung cancer cells [38].

$$\dot{y}_{PGE2} = k_{PGE2\_LCC} x_{LCC} - d_{PGE2} y_{PGE2}$$

(12) TGF- β

CAFs secrete potent oncogenic molecules, such as TGF-β and hepatocyte growth factor (HGF) [2].

Non-small lung carcinoma(NSCLC) cells lines produce both isoform of TGF-β [39].

TGF-β1 protein and messenger RNA (mRNA) expression are reported within bronchial epithelial cells [40].

$$\dot{y}_{TGF-\beta} = k_{TGF-\beta\_LCC} x_{LCC} + k_{TGF-\beta\_CAF} x_{CAF} + k_{TGF-\beta\_Epith} x_{Epith} + k_{TGF-\beta\_M2} x_{M2} - d_{TGF-\beta} y_{TGF-\beta}$$

(13) SDF-1/CXCL12

Secretion of SDF-1 by CAFs enhances the recruitment of endothelial progenitors into the tumor, promoting tumor vascularization [2].

$$\dot{y}_{SDF-1} = k_{SDF-1\_CAF} x_{CAF} + k_{SDF-1\_LCC} x_{LCC} - d_{SDF-1} y_{SDF-1}$$

(14) M-CSF

IL-1β can induce lung epithelial cells to release granulocyte macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) [31].

$$\dot{y}_{M-CSF} = k_{M-CSF\_Epith} x_{Epith} \left(1 + \frac{u_{M-CSF\_IL-1\beta} y_{IL-1\beta}^{n_{M-CSF\_IL-1\beta}}}{s_{M-CSF\_IL-1\beta}^{n_{M-CSF\_IL-1\beta}} + y_{IL-1\beta}^{n_{M-CSF\_IL-1\beta}}}\right) - d_{M-CSF} y_{M-CSF}$$

(15) GM-CSF

IL-1β can induce lung epithelial cells to release granulocyte macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) [31].

Cultured lung AC cells produce several macrophage chemoattractants, including IL-1β and GM-CSF [11].

$$\dot{y}_{GM-CSF} = k_{GM-CSF\_LCC} x_{LCC} + k_{GM-CSF\_Epith} x_{Epith} \left(1 + \frac{u_{GM-CSF\_IL-1\beta} y_{IL-1\beta}^{n_{GM-CSF\_IL-1\beta}}}{s_{GM-CSF\_IL-1\beta}^{n_{GM-CSF\_IL-1\beta}} + y_{IL-1\beta}^{n_{GM-CSF\_IL-1\beta}}}\right) - d_{GM-CSF} y_{GM-CSF}$$

(16) MCP-1/CCL2

CAFs secrete MCP-1 (CCL2), IL-6 and TNF-α, driving M1 to the M2 phenotype [2]. TGF-β is an important angiogenic factor and induces MCP-1 expression in ECs [41].

$$\dot{y}_{MCP\text{–}1} = k_{MCP\text{–}1\_CAF} x_{CAF} - d_{MCP\text{–}1} y_{MCP\text{–}1}$$

(17) IFN-γ

IFN-γ is produced by T cells upon cue from IL-12 and MHC displayed on the membrane of M1; M2 inhibits production of IFN-γ by T cells [42].

$$\dot{y}_{IFN-\gamma} = k_{IFN-\gamma\_T} x_T \left(\frac{x_{M1}}{s_{IFN-\gamma\_M1} + x_{M1}}\right)\left(\frac{s_{IFN-\gamma\_M2}}{s_{IFN-\gamma\_M2} + x_{M2}}\right) - d_{IFN-\gamma} y_{IFN-\gamma}$$

(18) TNF-α

IL-10 inhibits the production of TNF-α by M1 [43, 44].

$$\dot{y}_{TNF-\alpha} = k_{TNF-\alpha\_M1} x_{M1} \left(\frac{s_{TNF-\alpha\_IL\text{–}10}^{n_{TNF-\alpha\_IL\text{–}10}}}{s_{TNF-\alpha\_IL\text{–}10}^{n_{TNF-\alpha\_IL\text{–}10}} + y_{IL\text{–}10}^{n_{TNF-\alpha\_IL\text{–}10}}}\right) + k_{TNF-\alpha\_CAF} x_{CAF} - d_{TNF-\alpha} y_{TNF-\alpha}$$

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