**Detailed reactions and model equations for the manuscript titled ‘Tumor microenvironment governs the prognostic landscape of immunotherapy for head and neck squamous cell carcinoma: A computational model-guided analysis’**

A diagram of a complex structure

Description automatically generated with medium confidence

**Fig 1. Detailed HNSCC TME network model:** The nodes are either the cell states or the molecular species, whereas the edges represent diverse forms of interactions. The acronyms C\_0, C\_PDL1+, and C\_PDL1- refer to stem, PDL1+ (programed death ligand1), and PDL1- tumor cells, respectively. T\_K+, T\_K-, T\_Help, T\_Reg, and T\_Ex stands for PD1+ (programmed death 1), PD1- killer T cells, Helper T cells, Regulatory T cells, and Exhausted T cells, respectively. M\_1 and M\_2 refer to macrophages of M1 and M2 phase, respectively. Further, F\_WT and CAF correspond to wild type and invasive cancer associated fibroblasts, respectively. The acronyms IL-2, IL-8, IL-10 LIF, IFNG, IRF8, OPN, ICAM1, and Lac denote Interleukin-2, Interleukin-8, Interleukin-10, Leukemia Inhibitory Factor, Interferon Gamma, Interferon Regulatory Factor-8,  Osteopontin, Intercellular Adhesion Molecule-1, and Lactate, respectively.

We here lay out the kinetic rules imposed on the HNSCC TME network in Fig. 2. Before we proceed, we list out the necessary notations.

**Table 1:** Mathematical representation of the fluxes

|  |  |
| --- | --- |
| **Reaction flux** | **Mathematical expression** |
| Proliferation of CST () | Proportion of CAF engaged in barrier formation  Barrier formation rate |
| Exhausted T-cells-driven proliferation modulator of tumor cells |  |
| CAF-driven proliferation modulator of T-exposed Tumor cells |  |
| Conversion from CST to CNPDL1 |  |
| Conversion from CST to CPDL1 |  |
| Killer T cell-driven elimination |  |
| Death of CST |  |
| Proliferation of CSNT |  |
| Exhausted T cell-driven proliferation for immune inaccessible tumor cells | Width of CAF barrier, : proportion of CAF engaged in barrier forming |
| CAF-driven proliferation for immune inaccessible tumor cells |  |
| Conversion from immune inaccessible stem to immune inaccessible tumor cells |  |
| Conversion from immune inaccessible stem to immune inaccessible PDL1+ tumor cells |  |
| Killer T cell-driven elimination of immune inaccessible tumor stem cell |  |
| Death of immune-inaccessible stem cells |  |
| Resource-driven growth of PDL1- immune-accessible tumor cells |  |
| Killer T cell-driven elimination of PDL1- immune-accessible tumor cells |  |
| Conversion from PDL1- to PDL1+ tumor cells |  |
| Death of PDL1-, immune-accessible tumor cells |  |
| Resource-driven growth of PDL1+, immune-accessible tumor cells |  |
| Killer T cell-driven elimination of PDL1+ immune-accessible tumor cells |  |
| Death of PDL1+, immune-accessible tumor cells |  |
| Resource-driven growth of PDL1-, immune-inaccessible tumor cells |  |
| Death of PDL1-, immune-inaccessible tumor cells |  |
| Killer T cell-driven elimination of immune-inaccessible, PDL1- tumor cells |  |
| IFNG-induced conversion to PDL1+ immune-inaccessible  Tumor cells |  |
| Resource-driven growth of PDL1+, immune-inaccessible tumor cells |  |
| Death of PDL1+, immune-inaccessible tumor cells |  |
| Proliferation of Killer PD1+ T cells |  |
| M1 macrophage , Helper-driven growth of Killer T cells |  |
| IL2-driven growth of Killer T cells |  |
| Effect of anti-PD1(u): Conversion from PD1+ to PD1- killer T cell | Anti-PD1 dosage |
| Exhaustion rate |  |
| Death rate of PD1+ killer T cell |  |
| Proliferation of PD1- Killer T cells |  |
| Helper-driven growth of Killer T cells |  |
| Death rate of PD1- Killer T cells |  |
| Proliferation rate of helper T cells |  |
| Growth via antigen sensing |  |
| Regulator-driven inhibition |  |
| Death of helper T cells |  |
| Proliferation of regulatory T cells |  |
| CAF-driven proliferation of Regulatory T cells |  |
| Death rate of Regulatory T cells |  |
| Proliferation of exhausted T cells |  |
| Death rate of exhausted T cells |  |
| Proliferation of wild-type fibroblasts |  |
| Conversion from wild type to invasive fibroblasts | Proportion of LIF in contact with FWT |
| Death of wild type fibroblasts |  |
| Proliferation of invasive fibroblasts |  |
| OPN-induced growth of invasive fibroblasts |  |
| M2 macrophage-induced growth |  |
| Tumor cells-driven growth |  |
| Conversion from invasive to wild type fibroblasts |  |
| Death of invasive fibroblasts |  |
| Proliferation of M1-macrophages |  |
| Proliferation of M1 macrophage via antigen-sensing |  |
| Conversion from M1 to M2 macrophage | Proportion of IL-10 in contact with MACM1 |
| Conversion from M2 to M1 macrophage |  |
| Death of M1 macrophage |  |
| Proliferation of M2 macrophage |  |
| CAF-driven growth of M2 macrophage |  |
| Death of M2 macrophage |  |
| IL-2 secretion by Killer Cells |  |
| Degradation of IL-2 |  |
| LIF secretion by CAF |  |
| LIF secretion by Tumor cells |  |
| Degradation of LIF |  |
| IFNG secretion by T cells |  |
| Inhibition of IFNG secretion by OPN | : Proportion of OPN in contact with IFNG |
| Degradation of IFNG |  |
| IL-8 secretion by M2 macrophage |  |
| IL8-secretion by CAF |  |
| IL8-secretion by tumor cells |  |
| Degradation of IL8 |  |
| Lactate secretion by tumor cells |  |
| Lactate secretion by M2 macrophage |  |
| Lactate degradation |  |
| IL10 secretion by Killer T cells |  |
| Degradation of IL10 |  |
| ICAM1 secretion by Killer T cells |  |
| ICAM1 degradation |  |
| OPN secretion by CAF |  |
| OPN secretion by tumor cells |  |
| Inhibition of OPN secretion by IRF8 | : Proportion of IRF8 in contact with OPN |
| Degradation of OPN |  |
| IRF8 secretion by M1 macrophage |  |
| Degradation of IRF8 |  |

**Model equations:** Given the fluxes in Table 1, we construct the overall mathematical model for the HNSCC TME

**Abbreviations:**

CST= T-exposed Tumor stem cells

CSNT= Non T-exposed Tumor stem cells

CNPDL1= Tumor cells exposed to T-cells without pdl1

CPDL1= Tumor cells exposed to T-cells with pdl1

CRNPDL1= Tumor cells hidden from T-cells without pdl1

CRPDL1= Tumor cells hidden from T-cells with pdl1

Res= Resource concentration

TKPD1= Killer T cells with pd1

TKNPD1= Killer T cells without pd1

TH= Helper T cells

TREG= Regulatory T cells

TEX= Exhausted T cells

FWT= Wild type fibroblasts

CAF= Invasive cancer associated fibroblasts

MACM1= M1 phase macrophage

MACM2= M2 phase macrophage

IL2= Interleukin 2

LIF= Leukemia inhibitory factor

IFNG= Interferon gamma

IL8= Interleukin 8

LAC= Lactate

IL10= Interleukin-10

OPN= Osteopontin

IRF8= Interferon regulatory factor 8