**Table 1: Tumor modulating functions of different components of TME [3,5,36]**

|  |  |  |
| --- | --- | --- |
| Sl No | Tumor microenvironment component | Function associated with tumor progression |
| 1. | Stromal Component/ CAF Component | 1. Tumor growth and proliferation 2. Epithelial-mesenchymal transition 3. Metastasis associated phenotypes 4. Stemness of tumor niche 5. Stromagenesis 6. Evasion of immune surveillance and development of immune tolerance 7. Tumor induced angiogenesis 8. Tumor metabolism and drug resistance 9. Anti-tumour Activity |
| 2. | Extracellular matrix | 1. Controls availability, absorption, distribution, penetration and pharmacological metabolism of anti-cancer drugs 2. Stemness for tumor invasion 3. Pathways for tumor invasion |
| 3. | Vascular component | 1. Epithelial-mesenchymal transition 2. Metastasis associated phenotypes 3. Tumor induced angiogenesis |
| 4. | Tumor Immune microenvironment | 1. Immune surveillance |

**Table 2: Various signaling pathways involved in activation and function of Cancer associayted Pathways.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Signalling Pathways** | **Mediators** | **References** |
|  | TGF-β | * SMAD * bone morphogenetic protein (BMP) | [18, 118,119] |
|  | NF-κB signaling pathway | * TNF-α, IL-1β and their receptors, Toll-like receptors (TLRs), TNFR, and IL-1R * ligands such as CD40 | [120, 121, 122] |
|  | PI3K/AKT/mTOR signaling pathway | * tumor-derived exosomal miRNA-21 * Bone Morphogenetic Protein (BMP) * B7-H3 | [123,124, 125,126, 127,128] |
|  | Notch signaling pathway | - | [129] |
|  | MAPK signalling pathway | * ERK as the mitogen-responsive MAPK * JNK and p38 as the stress-responsive MAPK * Via miR-211 targeted insulin-like growth factor 2 receptor | [130, 131,132] |
|  | Wnt signalling pathway | * β-catenin, periostin * FZD receptors or ROR1/ROR2/RYK coreceptors | [133, 134, 135, 136, 137] |
| **7.** | JAK/STAT signalling pathway | * IL-6, IL-10, IL-11, and IL-22 * miR-210 * p53 | [138, 139, 140, 141] |
| **8.** | EGFR signalling pathway | * amphiregulin, betacellulin, EGF, heparin-binding EGF-like growth factor, TGF-α, epiregulin, epigen, and NRGs | [142, 143] |
| **9.** | Hippo signalling pathway | * regulated by upstream signals | [144, 145] |
| **10** | Erythrophoyetin-producing human hepatocellular (Eph) receptor pathway | * Ephrin | [146] |
| **11** | Shh signal pathway | * Hedgehog receptor Smoothened (SMO) | [147,148] |

**Table 3: Functional attributes, markers and proteins secreted, and signaling pathways of various CAF phenotypes in different tumor tissues.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Sl No** | **CAF Phenotype** | **Markers and proteins secreted** | | **Signalling pathways** | **Function** | **Reference** |
| 1. | iCAF  (Inflammatory CAF) | * IL-6, IL-11, IL-8 * CCL-2, CCL-17, CCL-22 * CXCL-1, CXCL-12 * LIF * Ly6c1, FBLN1 | | NF-κB Signaling | Migration/invasion/  metastasis  Angiogenesis  Immunomodulation/ Immunosuppression | [90, 177, 182, 183, 209,210,211] |
| 2. | my CAF  (myofibroblast) | * Collagen * POSTN * TGF-β * RGS5 | | TGF-β and IL-1/ JAK-STAT signalling | Migration/invasion/  metastasis  Proliferation  Chemoresistance | [90, 177, 182, 183, 210, 212] |
| 3. | apCAF  (Antigen presenting CAF) | * MHC-II * CD-74 * Serum Amyloid A3 * PDPN, COL1A2 * H2-Aa, H2-Ab1 | | MTORC1 signalling | Immunomodulation/  Immunosuppression  (decoy receptors to inhibit optimal T cell response) | [182, 183, 212] |
| 4. | rCAF  (Meflin + Cancer restraining CAF)  pCAF  (α-SMA+ cancer promoting CAFs) | * α-SMA -/Low (-/low) * Meflin+ (high) * PDPN * α-SMA+ (High) * Meflin--/low (-/low) | |  | Anti-tumorigenic | [213, 214] |
| 5. | CAF   * SI * S2 * S3 * S4 | Based on expression of FAP-α,  α-SMA, FSP-1, PDGF α/β and Caveolin | S1- TGF-β signaling, CXCL12 signaling  -  -  S4- NOTCH signalling | | S1- proliferation,  migration, invasion  metastasis and  immunosuppression  S4- proliferation,  migration, invasion,  and metastasis | [215,216, 217, 218] |
| `6 | Nephrilysin (CD-10) and G-Protein receptor 77 (GPR77) positive CAF | * CD10 * GPR77 | p65 driven NF-κB Signaling | | Chemoresistance &  cancer stemness  Proliferation | [219] |
| 7. | CAF-A  CAF-B | * MMP2, DCN, COL1A2 * α-SMA; TAGCN; PDGFA |  | | ECM remodelling  Myofibroblast-like | [220] |
| 7 | CAF-1  CAF-2 | * FSP-1, VEGF, TNC * Α-SMA, NG2, PDGFRβ |  | | Angiogenesis, metastasis  Physical barrier, Immunosuppression | [221] |
| 8 | vCAFs  mCAFs  dCAFs | * PDGFR-α, Nidogen-2, desmin, CD-31, MCAM, IL-6 * PDGFR-α, Fibulin-1, POSTN; COL5A1 * PDGFR-α, SCRG1 | PDGF-CC signalling  PDGF-CC signalling  PDGF-CC signalling | | Angiogenesis  Immunosuppression  Migration | [178, 222] |
| 8 | Podoplanin expressing CAF(PDPN+ CAF) | * PDPN | RHO-A activity | | Tumor cell invasion | [223] |
| 9 | H-CAF | * IL-6 & HGF | IL-6/STAT3-dependent pathway | | Epithelial-mesenchymal transition | [224] |