Cancers do not arise within a vacuum; rather they develop and grow within complex organs and tissue environments that critically regulate the fate of tumor cells at each sequential step of malignant progression. The tumor microenvironment (TME) can be viewed as an intricate ecosystem populated by diverse innate and adaptive immune cell types, stromal cells, extracellular matrix, blood and lymphatic vessel networks that are embedded along with the cancer cells. While bidirectional communication between cells and their microenvironment is critical for normal tissue homeostasis, this active dialog can become subverted in cancer leading to tumor initiation and progression. Through their exposure to tumor-derived molecules, normal cells can become “educated” to actually promote cancer development. As a consequence of this tumor-mediated education, TME cells produce a plethora of growth factors, chemokines, and matrix-degrading enzymes that together enhance the proliferation and invasion of the tumor. Moreover, these conscripted normal cells also provide a support system for cancer cells to fall back on following traditional therapies such as chemotherapy and radiation, and additionally contribute to a general immune-suppressive state, thus limiting the efficacy of immunotherapies. Consequently, multi-targeted approaches in which co-opted cells in the microenvironment are “re-educated” to actively fight the cancer represent a promising strategy for the effective long-term treatment of this devastating disease.

**ABSTRACT**

Cancers do not arise within a vacuum; rather they develop and grow within complex organs and tissue environments that critically regulate the fate of tumor cells at each sequential step of malignant progression. The tumor microenvironment (TME) can be viewed as an intricate ecosystem populated by diverse innate and adaptive immune cell types, stromal cells, extracellular matrix, blood and lymphatic vessel networks that are embedded along with the cancer cells. While bidirectional communication between cells and their microenvironment is critical for normal tissue homeostasis, this active dialog can become subverted in cancer leading to tumor initiation and progression. Through their exposure to tumor-derived molecules, normal cells can become “educated” to actually promote cancer development. As a consequence of this tumor-mediated education, TME cells produce a plethora of growth factors, chemokines, and matrix-degrading enzymes that together enhance the proliferation and invasion of the tumor. Moreover, these conscripted normal cells also provide a support system for cancer cells to fall back on following traditional therapies such as chemotherapy and radiation, and additionally contribute to a general immune-suppressive state, thus limiting the efficacy of immunotherapies. Consequently, multi-targeted approaches in which co-opted cells in the microenvironment are “re-educated” to actively fight the cancer represent a promising strategy for the effective long-term treatment of this devastating disease.