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Modeling of Chemotherapy in Combination with Modulation of Tumor-Associated Macrophage Interactions in the Tumor Microenvironment

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Chemotherapy has been a primary means to treat cancer in advanced stages, including metastatic disease. Unfortunately, outcomes have often disappointed across a variety of cancer types. Recently, the role of the immune system cells in the tumor microenvironment in promoting or inhibiting tumor progression has come under renewed scrutiny. Therapeutic manipulation of tumor-associated macrophages may hold promise to potentiate their contribution towards sustained tumor suppression. However, the interactions of the immune system cells with the tumor microenvironment and the associated effects on chemotherapeutic outcomes remain poorly understood. This type of complex system could benefit from mathematical modeling for improved system analysis. We develop a modeling framework to simulate interactions between immune system cells and tumor cells in the metastatic microenvironment typical of advanced cancer, with the capability to evaluate the associated effects on chemotherapeutic treatment. M1, M2, and Tie2 (TEM) expressing macrophage variants are integrated into a model of tumor growth representing a metastatic lesion in a highly vascularized organ, such as the liver. Behaviors simulated include M1 release of cytotoxic inducible nitric oxide synthase (iNOS), M2 release of growth-promoting factors, and TEM facilitation of angiogenesis via Angiopoietin-2 and promotion of monocyte differentiation into M2 via IL-10. The modeling results suggest that a more nuanced approach to influencing monocyte differentiation taking into account the tumor state, e.g., under chemotherapy, may be desirable. Accordingly, we explore potential synergistic outcomes of various macrophage manipulation therapies in combination with the common chemotherapeutic agent Gemcitabine.