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Exploring the Influence of the Total Target-Antigen Burden on CAR-T Cell Immunotherapy

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CAR-T cell immunoterapy stands out as a highly promising way in cancer treatment, receiving significant attention within the scientific community. This type of treatment aims to increase the ability of the patient's own immune system to fight tumor cells. T lymphocytes are extracted from the patient, genetically modified to express the CAR gene, expanded *ex vivo*, and reintroduced into the patient. These engineered cells are called CAR-T cells and possess enhanced ability to recognize and kill tumor cells expressing a specific target antigen [2]. In hematological cancers, affecting B cells, the target antigen is expressed by both malignant and healthy B cells, leading to a cytotoxic impact of CAR-T cells on both cell types. As a result of treatment, patients may develop B cell aplasia (BCA), a manageable side effect. Remarkably, BCA serves as a vital clinical marker, indicating the presence of functional CAR-T cells and enabling precise monitoring and management of the patient's treatment [1]. Here, our objective is to explore the role of healthy B cells expressing the target antigen in CAR-T cell immunotherapy through the development of a mathematical model. The system of equations, derived from a prior model [3] and incorporating the interaction mechanisms and variables illustrated in Figure 1(left), is presented as follows:

$$\frac{dC_D}{dt} = -(\beta+\eta)C_D \ ; \tag{1}$$

$$\frac{dC_T}{dt} = \eta C_D + \kappa(t)F(T,B)C_T - (\xi + \epsilon + \lambda)C_T + \theta(T+B)C_M - \alpha T C_T \ ; \tag{2}$$

$$\frac{dC_M}{dt} = \epsilon C_T - \theta(T+B)C_M - \mu C_M \ ; \tag{3}$$

$$\frac{dC_E}{dt} = \lambda C_T - \delta C_E \ ; \tag{4}$$

$$\frac{dT}{dt} = r_1 T(1-bT) - \gamma_1 f(C_F,T,B)T \ ; \tag{5}$$

$$\frac{dB}{dt} = r_2 B(1-bB) + B_p - \gamma_2 f(C_F,T,B)B - \omega T B \ . \tag{6}$$

The injected target antigen directed CAR-T cells (C_D) initially undergo rapid distribution throughout the patient's body, with a natural death rate of β. A portion of these cells engrafts into C_T at a rate η, establishing in the blood and tumor site, and proliferates upon encountering the target antigen at a patient-specific rate $\kappa(t)F(T,B)$, with $\kappa(t) = r_{min} + p_1\left[1+(p_2\ t)^{p_3}\right]^{-1}$ and $F(T,B) = (T+B)(A+T+B)^{-1}$ (see details in [3]). They differentiate into memory CAR-T cells at a rate ϵ, eventually dying naturally at a rate ξ, or being hindered by tumor-induced

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immunosuppression regulated by α. Both C_T and C_D are functional CAR-T cells (C_F) with cytotoxic effects. Long-term C_M can also die naturally at a rate μ but are readily responsive to antigen-expressing cells, potentially differentiating back into C_T when interacting with T and B at a coefficient θ, eliciting a rapid immune response against the tumor. Over time, C_T may become exhausted (C_E) and undergo apoptosis at a rate δ.

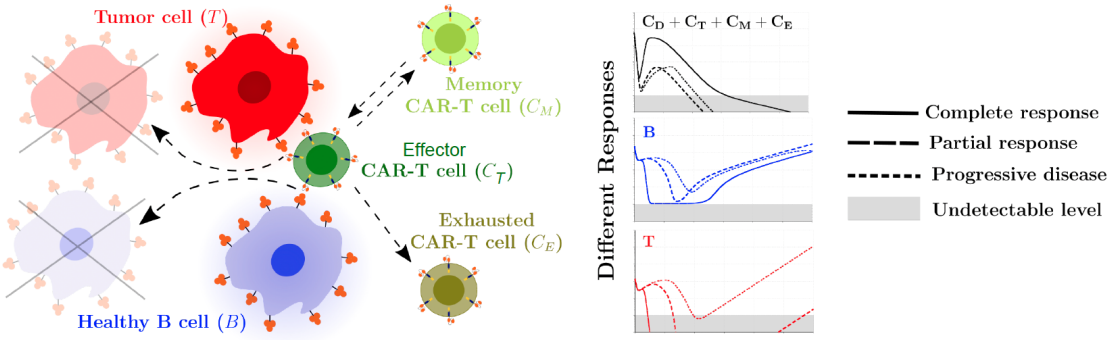

Figure 1: Interaction mechanisms and variables (left), and dynamics for different therapy responses (right).

Both T and B experience growth limited by available resources in the tumor microenvironment, sharing a common carrying capacity of $1/b$. Tumor cells exhibit a higher proliferation rate ($r_1 > r_2$) compared to healthy B cells due to their acquired functional capabilities during development. Functional CAR-T cells (C_F) exert cytotoxic effects on both T and B cells at rates γ_1 and γ_2, respectively, following a saturation function $f(C_F, T, B) = \dfrac{C_F}{T+B}\left[\vartheta + \dfrac{C_F}{T+B}\right]^{-1}$, where ϑ is a half-saturation constant. Notably, the cytotoxic impact of C_F on healthy B cells (γ_1) is greater than that on tumor cells (γ_2) because tumor cells can evade cytotoxic effects through various mechanisms, such as hiding target antigens temporarily. Additionally, healthy B cells receive a continuous supply of B cell precursors from the marrow (B_p) and compete with tumor cells under a competitive exclusion interaction with a rate of ω.

By calibrating the model for several datasets, we capture distinct dynamics, as illustrated in Figure 1(right), encompassing various compositions of CAR-T cell subpopulations and B cell aplasia periods, resulting in a range of therapy responses. Further analyses highlight how the model contributes to a greater understanding of the influence of the total target-antigen burden on therapy outcomes.

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