Cell-competition and stochastic extinction in chimeric antigen receptor T cell therapy

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Chimeric antigen receptor (CAR) T cell therapy is remarkably effective immunotherapy that relies on in vivo expansion of engineered CAR T cells, after lymphodepletion (LD) by chemotherapy. The quantitative laws underlying this expansion and subsequent tumor eradication remain unknown. We develop a mathematical model of T cell–tumor cell interactions and demonstrate that expansion can be explained by immune reconstitution dynamics after LD and competition among T cells. CAR T cells rapidly grow and engage tumor cells but experience an emerging growth rate dis- advantage compared to normal T cells. Since tumor eradication is deterministically unstable in our model, we define cure as a stochastic event, which, even when likely, can occur at variable times. However, we show that variability in timing is largely determined by patient variability. While cure events impacted by these fluctuations occur early and are narrowly distributed, progression events occur late and are more widely distributed in time. We parameterized our model using population-level CAR T cell and tumor data over time and compare our predictions with progression-free sur- vival rates. We find that therapy could be improved by optimizing the tumor-killing rate and the CAR T cells' ability to adapt, as quantified by their carrying capacity. Our tumor extinction model can be leveraged to examine why therapy works in some patients but not others, and to better understand the interplay of deterministic and stochastic effects on outcomes. For example, our model implies that LD before a second CAR T injection is necessary. Further, we seek to use these models to better predict which patients might benefit from cellular therapy, especially in light of their intrinsic tumor properties.

References

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