Modelling the role of cytotoxic T lymphocytes in tumour regression

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Thesis Summary

Immunotherapies for cancer are an emerging class of therapeutic strategies which aim to treat cancer via augmentation of the immune system. Despite significant success of immunotherapies in the past decade, not all patients will respond to these treatments and the reasons why immunotherapies are successful in some patients, but not others, remain incompletely understood. The immune response to cancer is a complex, multistage process, and mathematical and computational models are a useful tool for understanding such complex systems. In this thesis, I develop mathematical and computational models of Cytotoxic T Lymphocytes (CTLs), who are key players in the immune system due to their ability to recognise, destroy, and provide long lasting protection against malignant or virally infected cells.

Since the rate at which CTLs can kill tumour cells is a crucial parameter determining their efficacy in immunotherapies, in chapter 2, I ask how the killing rate of CTLs is best quantified based on imaging data. By developing Monte Carlo simulations of CTLs killing target cells, I show that population-level killing statistics can give misleading conclusions about the killing behaviour of CTLs. Specifically, I show how the results of an *in vitro* killing assay, purporting to demonstrate the existence of a subpopulation of “high rate killer” CTLs, could alternatively be explained by a homogeneous population of CTLs which require multiple hits with cumulative damage before target cells can be killed. I develop a bayesian inference procedure for estimating CTL killing parameters from imaging data, and validate this inference procedure using artificial data created with an agent based model.

In chapter 3, I ask whether the rate at which CTLs kill EL4 lymphoma cells, determined from *in vivo* two photon imaging experiments, is sufficient to explain EL4 tumour regression. To test this, I develop both an Ordinary Differential Equation (ODE) model and an Agent Based Model (ABM) to describe the interaction of adoptively transferred CTLs with the EL4 tumours. Based on the results of both models, I find that the measured killing rate of the CTLs is not compatible with tumour regression in the EL4 tumours. Using the ABM, I test alternative hypotheses which might explain how transferred CTLs could have led to tumour regression. I conclude that an antiproliferative effect associated with the transferred CTLs is compatible with the experimental data.

In chapter 4, I examine an *in vivo* data set of B16F10 melanoma treated with adoptively transferred CTLs that were stimulated with an agonist antibody targeting the CD137 receptor. I ask what were the primary mechanisms CTLs used to control the tumours, and also how the stimulation via the CD137 receptor altered the functions of the transferred CTLs. To address these questions, I developed an ODE model of the interaction between the transferred CTLs and the B16F10 tumours. Similarly to the EL4 tumours examined in chapter 3, I find that the killing rate of the transferred CTLs is insufficient to account for the reduced tumour progression after CTL transfer, and that a substantial antiproliferative effect exerted upon tumour cells is necessary to explain the data. Moreover, the results of the modelling study indicate that stimulation of the CTLs via their CD137 receptor enhances this antiproliferative effect, explaining the reduced tumour size in the CD137 stimulated condition relative to the non-CD137-stimulated control tumours.

In chapter 5 I revisit the B16F10 melanoma model using a different set of experimental data. Similarly to chapter 4, I develop an ODE model and apply it to the experimental data, confirming that the control of these B16F10 melanoma tumours after CTL transfer can largely be explained by an antiproliferative effect associated with the transferred CTLs. Accompanying the experimental data I employ in chapter 5 are longitudinal measurements of gene expression taken from the tumours. By integrating these gene expression data in the ODE model, I ask whether the transcriptional dynamics of the cytokine IFN-γ are compatible with the dynamics of the antiproliferative effect. This analysis shows that these dynamics are indeed compatible with each other, indicating that IFN-γ is plausibly the sole mediator of the antiproliferative effect in this *in vivo* set-up. IFN-γ transcription did not last for more than a few days in the data, indicating that the CTLs had lost their ability to control the tumours. Therefore I also searched within the gene expression data for the transcription of molecules that might explain the deactivation of the CTLs. I conclude that the dynamics of a number of immune checkpoint molecules are compatible with their role in shutting down the antitumour functions of the CTLs.

Overall, the results in this thesis suggest that computational models are a useful and appropriate tool for understanding the immune response to cancer. Moreover, I establish a framework for examining the effector functions of CTLs in the context of cancer immunotherapy. Using this framework, I identify an important contribution of a CTL mediated antiproliferative effect in two different experimental tumour cell lines. In the B16F10 melanoma model, I characterise the antiproliferative effect in further detail. I find it is consistent with CTL secretion of the cytokine IFN-γ, that it is enhanced by stimulation of CTLs via their CD137 receptor, but that it is also short-lived. Finally, I identify several immune checkpoint molecules associated with the termination of IFN-γ production.