Mathematical models for immune checkpoint therapy of cancer

Alan Rendall

Institut für Mathematik
Johannes Gutenberg-Universität Mainz

The immune system and cancer

- function of the immune system: fight infectious diseases
- dangerous bacteria, viruses etc. are rendered harmless
- can the immune system also fight cancer?
- this idea has been around for a long time
- Kaposi's sarcoma in AIDS patients
- can cancer therapies be developed using this idea?
- for many years all attempts basically failed
- recently positive results have been achieved
- now there are several successful therapies of this type
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T cells

- white blood cells (central elements of the immune system)
- an important class of these are the T cells
- they distinguish between foreign and host substances
- the first should be attacked, the second not
- not attacking foreign substances $\rightarrow$ dangerous infections
- attacking host substances $\rightarrow$ autoimmune diseases
- T cells have the responsibility for making this decision
- how is their activity controlled?

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Switching T cells on and off

- on the cell surface there is the T cell receptor
- antigen (foreign substance) $\rightarrow$ activating signal
- confirmation is required to avoid collateral damage
- second signal via CD28
- there is also an inhibitory signal via CTLA-4 (checkpoint)
- first therapy (ipilimumab) is an antibody against CTLA-4
- cure of 20% of patients with metastatic melanoma
- inhibitory signal via PD-1
- therapy (pembrolizumab) is an antibody against PD-1
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Interlude, big and small models

- big models with as many substances as possible
- suffer from large uncertainties
- small models try to isolate essential elements of the dynamics
- my interest is in small models and I believe both should be combined
- numerous clinical trials for immune checkpoint therapies
- the drug companies have their mathematical models
- they are big and not in the public domain
- talks at SMB meeting in Montreal by modellers from Genentech, Pfizer and Glaxo-Smith-Kline

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The model of Arulraj and Barik

- the unknowns come in three groups x_i, y_i und z_i
- system is partially decoupled
- $\dot{x} = f_1(x)$, $\dot{y} = f_2(x, y)$, $\dot{z} = f_3(x, z)$
- outputs of the system are components of y and z
- it make sense to first examine the model for the x_i
- variables PD-1, Shp2 (phosphatase), Lck (kinase)
- Lck comes in five different forms
- model for Lck on its own a paper of Rohrs et al.
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Insights into the mechanism

- Shp2 binds to PD-1 and gets activated
- Shp2 dephosphorylates CD28 (second signal switched off)
- dephosphorylation of the T cell receptor of secondary importance
- mathematical model says, that a second mechanism is also important
- Shp2 dephosphorylates Lck, which weakens other parts of signal transduction (influence on z)
- two-dimensional pictures of response functions

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- effective in B cell leukemia in children
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