Direct T cell mediated killing in solid tumours is insufficient to explain tumour regression

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Immunotherapy in Cancer

- Activating and enhancing anti-tumour response
- Adoptive cell transfer
- Modelling to gain mechanistic insight and quantitative understanding

Investigating T cell killing rate in an in-vivo model of a solid tumour

- Killing rate: 3/day
- All deaths T cell mediated
- Low infiltration (E:T ≈ 1:100)
- Is this sufficient for tumour regression?

Data overview (growth rate)

- Tumour cell replication rate estimated from growth rate of untreated tumours
- Tumour cell density used to estimate number of cells

Data overview (Tcells)

- CTL density is known
- T Cells remain even in areas where tumour has disappeared

Ordinary Differential Equation model

\[ \frac{dT}{dt} = gT - kE \]
\[ \frac{dD}{dt} = kE \]

\[ E = \rho_E V_c (D + T) \]

\{T, D > 0\}
Ordinary Differential Equation model results

- Regression not achieved with killing rate 3/day
- Killing rate 10-fold higher required
Agent based model

- More accurately quantify contribution of direct killing
- Suggest additional mechanisms
Agent based model

- Cells represented as grid points
- Tumour cells reproduce into neighbouring squares
- T Cells appear at random throughout tumour
- T cells kill single target over 8 hrs
Agent based model - results

The diagrams show the growth of tumour size over days after tumour injection. The x-axis represents days after tumour injection, and the y-axis represents the number of cells. Different lines represent different growth rates (k values), with varying colors and labels.

The diagrams illustrate how the tumour size changes over time with different growth rates, highlighting the impact on tumour growth.

Legend:
- k.003
- k.020
- k.040
- k.060
- k.080
- k.120
- no.CTL

Growth is depicted by the red dots and arrows connecting the yellow and black portions of the diagrams.
CTL induced cell cycle arrest

- T Cells produce IFN\(\gamma\)
- IFN\(\gamma\) causes cell cycle arrest
- Shown to be important in ACT tumour control

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