



# Dynamics of Naive T lymphocyte Quiescence Exit

## ABSTRACT

Naive T lymphocytes are cells of the adaptive immune system that remain in a non-dividing or quiescent state. Antigen exposure triggers their quiescence exit and cell cycle entry. There are two types of naive T lymphocytes viz the CD4+ or Helper T cells and the CD8+ or Cytotoxic T cells. However, they differ in signalling requirements and response time for the first division. Understanding the dynamics of quiescence exit and unfolding the differences between CD4+ and CD8+ T cells can aid the therapy of autoimmune and immunodeficiency disorders. We propose depth of quiescence quantified by the ratio of cell cycle inhibitors and activators as a crucial regulator of response dynamics.

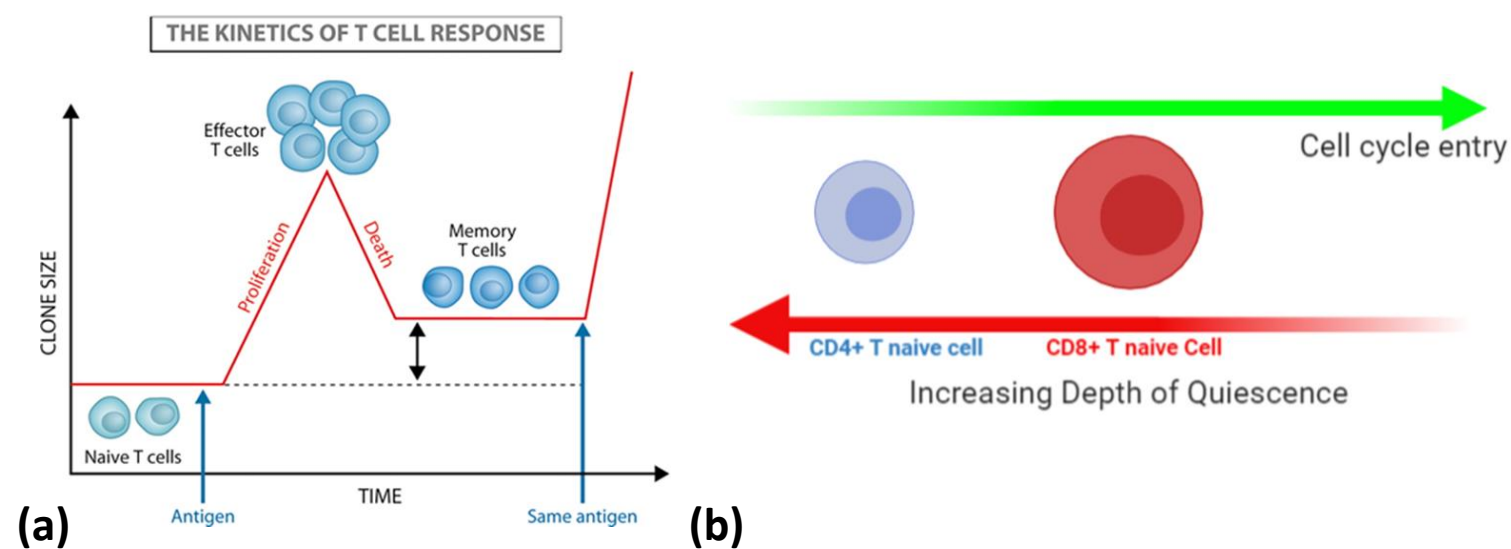


Fig. 1: (a) Kinetics of T cell response (reproduced from Valujskikh et al, 2007); (b) proliferative advantage of CD8+ over CD4+ T cells.

## OBJECTIVE

- Development of wiring diagram to capture naïve T lymphocyte activation dynamics.
- Mathematical modeling of quiescence(G0) exit and early cell cycle (G1 phase, G1/S transition).
- Analysis of transcriptomics and proteomics data to explore the differences between cell types.
- Propose hypothesis to build a consensus across experimental studies, pave path for future experiments.

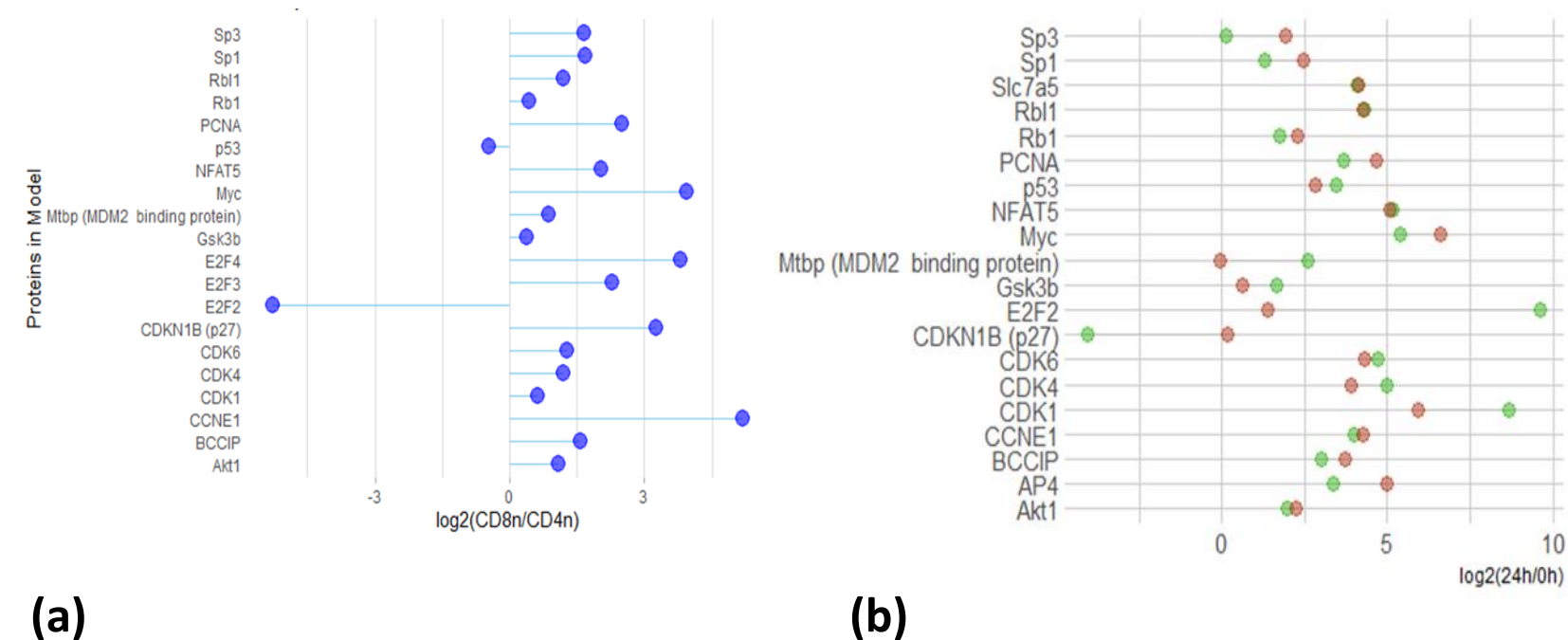


Fig. 3: Lollipop plot of (a) relative ratio of protein abundance in CD8+ versus CD4+ T cells in naïve state. Positive values denote CD8+ cells have active translational machinery compared to CD4+ cells in naïve state; (b) log fold change in protein levels after 24 hrs of TCR stimulation. For most of the proteins, CD8+ T cells undergo rapid rise in protein accumulation. Expression data serves as the basis for depth of quiescence modeling (Fig. 4a).

## RESULTS

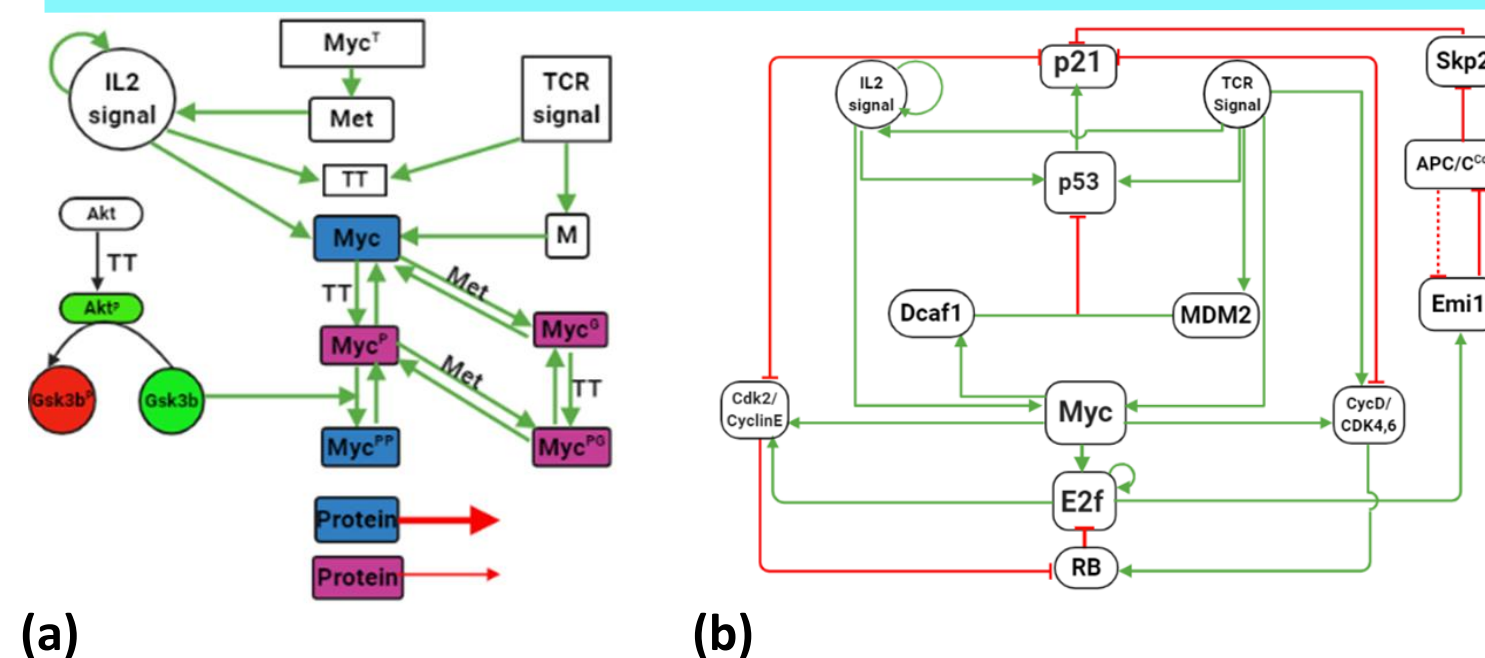


Fig. 2: Wiring diagram of (a) T cell activation and G0 exit on antigen exposure (TCR – T cell receptor complex, IL2 – Interleukin 2); (b) G1 phase and G1/S transition post G0 exit.

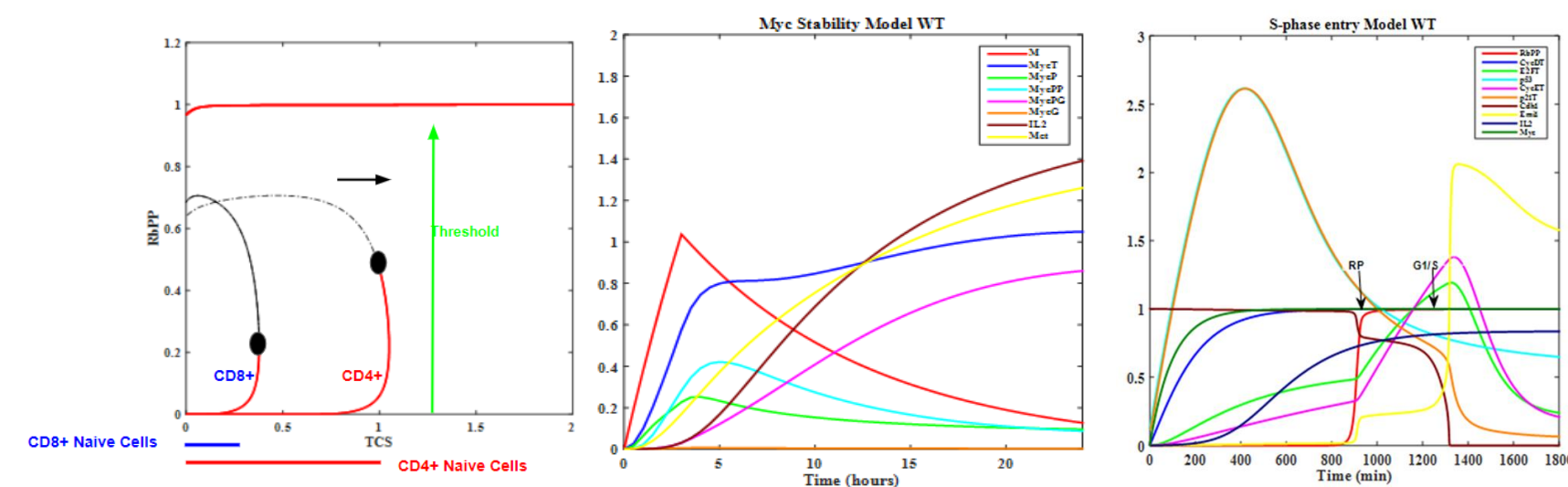


Fig. 4: (a) Higher barrier (cell cycle inhibitors vs. activators) push CD4+ naïve T cells into deeper quiescence, the strength of T cell signal required for activation increases with depth of quiescence. Temporal dynamics of (b) G0 exit on antigen exposure; (c) G1 phase and G1/S transition post G0 exit.