mRNA as a molecular clock: how mRNA longevity controls the persistence of cellular information

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Short Abstract — How cells translate short-lived signaling events to long-term responses constitutes a fundamental problem in biology. Recent work indicates that T-cells form short-lived conjugates with antigen presenting cells and secrete cytokines before dissociation. We focused on tumor antigen presentation in response to T-cell derived Interferon-γ (IFN-γ). We hypothesized that tumor cells may employ mechanisms to extend transient IFN-γ signaling to maintain antigen presentation on longer time-scales. By coupling experiments and mathematical modeling, we identified mRNA lifetime as the critical parameter controlling the longevity of antigen presentation. This work uncovers how a basic biochemical parameter can govern the persistence of cellular information.

Keywords — antigen presentation, tumor immunology, cytokine signaling, systems biology

I. INTRODUCTION

Recent studies have highlighted the transient and directional nature of IFN-γ secretion by activated T-cells [1,2]. T-cells encounter antigen presenting cells (APC), arrest, become activated, and secrete IFN-γ towards the APC for a timescale on the order of 2-6 hours. Shortly after, T-cells express inhibitory molecules, which attenuate the interaction and halt cytokine production. Antigen presentation is an important parameter determining tumor rejection by T-cells so we focused our efforts on tumor MHC class I regulation in response to IFN-γ.

Since IFN-γ signaling is short-lived but many immune responses occur on the time-scale of 2-6 days, we conjectured that cytokine-responding cells employ mechanisms to extend the signal beyond the order of hours to maintain elevated antigen presentation.

II. RESULTS

To test this hypothesis, we cultured melanoma cells with dose-titrations of IFN-γ and extinguished the signal at varying times after exposure. Surprisingly, cells up-regulated MHC-I that scaled with the initial quantity of IFN-γ for 15-20 hours following signal abolishment. This phenomenon was not attributable to a lengthy signal transducer lifetime or synthesis of a signal-extending protein. Cells preserved information regarding the quantity of their stimulus for at least a day after the signal was gone.

To probe molecular mechanisms that could account for these observations, we constructed an ODE-based computational model of MHC-I transcription, translation, and decay. Our model predicted that the key parameter responsible for MHC-I memory for IFN-γ is an extraordinarily long mRNA lifetime.

We measured the decay of MHC-I mRNA following signal abolishment and calculated a half-life of 35 hours – nearly 4 times the median global mRNA half-life of 9 hours [4].

To uncover the functional significance of this lengthy mRNA lifetime, we used our model to quantify the presentation of new antigen per cell over a 2 day time period when mRNA half-life was either 35 hours, or set to the global median. Our model predicted a loss of 200-600 antigen per minute, and greater than one million when integrated over 2 days – a feature likely to profoundly impact subsequent T-cell encounters.

III. CONCLUSION

This mechanism guarantees that cells can preserve and amplify signals from a transient burst of cytokine emitted by a neighboring T cell. In addition, by fine-tuning the level of surface MHC-I expressed, cells can maintain a balance between acquiring susceptibility to T cell killing, while losing their vulnerability to cidal NK cell activity. Finally, these results provide a mechanism to account for the general problem of how cells link long-term phenotypic outcomes to short-lived signaling responses [4].

REFERENCES