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Can polyclonality prevent the outbreak of leukemia?

T cell receptor (TCR) polyclonal mature T cells are surprisingly resistant to oncogenic transformation through retroviral induction of T cell oncogenes. It has been shown that leukemia/lymphoma did not occur upon transplantation of polyclonal T cells into RAG1-1-deficient recipients, although the T-cells were transduced with high copy numbers of gammaretroviral vectors encoding potent T cell oncogenes [1]. Further studies demonstrated that the transplantation of T cells from TCR monoclonal OT1 mice that were transduced with the same protocol resulted in leukemia/lymphoma. The underlying mechanisms that prevent oncogenesis in the polyclonal situation and endorse the outbreak of leukemia in the monoclonal situation are currently unclear.

Using a mathematical modeling approach, we challenge the arising hypothesis that polyclonality induces competition within the T cell repertoire, which in turn suppresses the emergence of a leukemic clone. As a starting point, we developed a simple model of T cell homeostasis emphasizing the analogy of T cell homeostasis to species coexisting in ecological niches. The key assumption of the model is that T cell survival is critically dependent on the interaction of the clone-specific TCR with self-peptide-MHC-complexes (corresponding to environmental niches).

Based on our modelling results, we speculate about the cellular properties of the leukemic clone. Within our model framework, we are able to explain the observed phenomena under the following two assumptions about the cellular properties of the leukemic clone: (i) The leukemic clone is less competent than other T cell clones in acquiring survival stimuli from niches. (ii) Proliferation of the leukemic clone is less dependent on niche interaction. This is a plausible assumption as the transgenes are potent oncogenes capable of activating mitotic pathways.

From our results we conclude, that clonal competition is a possible mechanism to counterbalance clonal dominance. Our modeling results allow us to foster the design of further biological experiments. A future goal is to determine the minimum clonal complexity that is needed in order to control the leukemic clone under the given circumstances.

References

[1] Newrzela S, Cornils K et al. Resistance of mature T cells to oncogene transformation. Blood. 2008;112(6):2278–2286.