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Why the immune system takes its chances with randomness

Philip D. Hodgkin, Mark R. Dowling and Ken R. Duffy

In their recent Opinion article (Lymphocyte fate specification as a deterministic but highly plastic process. *Nature Rev. Immunol.* **14**, 699–704 (2014))[1], Reiner and Adams presented a fascinating deterministic interpretation of how lymphocytes acquire different fates. They propose that the generation of multiple lymphocyte subsets from each precursor occurs via an inevitable developmental pathway. This deduction is based on the premise that the system is too important to be left to stochastic processes. To account for recent evidence to the contrary, stochastic processes are suggested to only appear under conditions in which artificially large numbers of responding precursors might relax the deterministic programme (as used in REFS 2,3) or under *in vitro* conditions in which the usual three-dimensional (3D) arrangement of externally delivered signals that channel fates is removed (as used in REF. 4). In other words, stochastic mechanisms only occur when experimental conditions happen to support the role of randomness.

There are, however, several reasons — as outlined below — to challenge the premise that stochastic processes are not equally up to the task of generating a reliable immune response.

Precedent

The authors themselves point out that evolution exploits randomness for the most important task of all — creating lymphocyte receptor diversity. Other immune examples of stochastic processes include the probabilistic expression of cytokines[5,6] and the combinatorial expression of natural killer cell receptors in a population[7].

Efficiency

In the imagined B cell and T cell odysseys[1], at least six intricate moves must take place to generate the different cell fates. A distinct deterministic pathway is needed for each, and the correct set of signals must be received in the correct order by each of potentially thousands of progeny; lymphocytes and numerous other cells must encode complex instructions for orchestrating the right set of signals to generate every cell type at the right time. By contrast, by using stochastic processes multiple cell types can be generated with much simpler instructions[4,8–11], even in the absence of environmental direction.

Reductionism

It is tempting to observe the complex structures and cell interactions of primary lymphoid tissue and deduce that they are crucial for the formation of heterogeneous outcomes. This hypothesis has been tested by asking what remains when such structures are removed. We and others find a great deal of cell fate heterogeneity under simple *in vitro* culture conditions[4–6,12,13]. Conversely, crucial molecular contributors to early developmental programmes, including asymmetric cell division, do not alter B cell or T cell responses *in vivo*[14]. Thus, although the 3D environment and asymmetric programming might have some role in modifying cell fate allocation, they are not the only sources of variation.

Extrapolation

In the stochastic interpretation, variation is inherent and consistent immune outcomes only arise when considering the population as a whole. As Reiner and Adams point out, the number of antigen-specific precursors recruited into the immune response is a crucial variable, and may be as low as 20. However, mathematical models in which randomness drives cell fate selection suggest that a reasonably robust immune response can be achieved even with starting cell numbers of this order[4,9,10,15]. Thus, a role for randomness should not be rejected on this basis alone.

Summary

As a research community, we have not yet acquired all of the data required to answer how both deterministic and stochastic processes interleave to build the complete immune response. However, along with Reiner and Adams, we look forward to the resolution of this conundrum. Perhaps unlike them, however, we are gamblers, suspecting that the immune system does play a game of chance, albeit with the rules having evolved so that the odds are stacked in our favour.

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Competing interests statement
The authors declare no competing interests.