Expression Diversity Adds Richness to T Cell Populations

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Variation in protein expression is a feature of all cell populations. Using T cell subsets as a proof-of-concept, Lu et al. (2016) develop a framework for dissecting out the contributors to this cell-to-cell expression variation from high-parameter flow cytometry studies.

Subsetting, one of the favorite pastimes of T cell immunologists, involves identifying clusters of cells with a distinct function and seemingly homogeneous expression profile. However, even within the most tightly defined populations, substantial heterogeneity in gene expression exists at the cell-to-cell level. This diversity arises due to stochastic processes, differential environmental input, and intrinsic differences in cellular history. Typically such heterogeneity is dismissed as noise; however, growing evidence indicates that such heterogeneity is dismissed as noise; thereby reducing required dose and, consequently, unit costs.

REFERENCES


regulatory mechanisms at play for even a single protein.

At least some of the differences in the cell-to-cell expression variation between different proteins are likely to have biological significance. When individuals of different ages were assessed for cell-to-cell expression variation, significant age-dependent changes were observed (Lu et al., 2016). For example, assessment of CCR7 expression of CD4+CD25+ regulatory T (Treg) cells, found higher levels of cell-to-cell variation in older persons when compared to young adults. As CCR7 is needed for lymphocyte migration, increased heterogeneity could influence the tissue homing behavior of Treg cells, altering the local balance between tolerance and immunity. It is possible that such differences in cell-to-cell expression variation could contribute to the functional degradation of immunity observed in older persons.

Genetic control over cell-to-cell expression variation was also observed. Lu et al. (2016) found ten unique interactions between cell-to-cell expression variation and genetic polymorphisms linked to (auto)immune conditions such as multiple sclerosis, asthma, rheumatoid arthritis, and Crohn’s disease. One striking example was the association of rs1588265, an intronic SNP in PDE4D, with the degree of cell-to-cell expression variation in HLA-DR on CD8 T cell subsets. The minor allele of rs1588265, protective against asthma, was associated with increased variation in HLA-DR expression (i.e., a broader spread of low- to high-expressing cells). Critically, this association could not have been picked up using classical approaches: the different alleles of PDE4D did not alter the mean expression of HLA-DR, impacting only on the cell-to-cell variation around the mean. While this association does not demonstrate that the minor allele of PDE4D confers protection to asthma through increasing the variability of HLA-DR expression, it does suggest that the degree of variation, as well as mean expression, might alter disease susceptibility or progression.

One of the major questions arising from this study is the relationship between cell-to-cell expression variation and T cell receptor (TCR) clonality. Due to genomic rearrangement, the TCR is distinct at the sequence level on a cell-to-cell basis between each newly generated T cell. Because TCR engagement is obligatory for T cell development, the differential affinity of TCR for self-antigen-MHC complexes can leave its imprint on “tuning” molecules, adjusting baseline signaling to a common tonic level (Davis et al., 2007). To what extent are the properties of cell-to-cell expression variation directed by TCR sequence differences? Is the observed variation inherited in a clonal manner, such that competition between activated T cells is driven by both TCR sequence difference and cell-to-cell expression variation in key molecules? It is distinctly possible that variation in the expression of key TCR signaling molecules is clonally inherited and enhances the functional diversity of T cells. Under this scenario, additional heterogeneity might increase the chance of a T cell undergoing productive stimulation, elevating the utility during infection. The corollary is also notable—increased expression diversity could elevate the risk of an inappropriate reaction. These same arguments have been made for TCR sequence diversity, where the reduction of thymic output with age might be an evolved response to the rising cost-benefit ratio of TCR diversity with age (Dowling and Hodgkin, 2009).

Beyond these findings, the current study provides a resource for other investigators to identify cell-to-cell variation changes that might have biological significance. These results are limited to the scope of markers used in the original study, and it is unclear to what extent the observed properties will be extended to other proteins. Because markers are a non-random set of proteins, the original selection might have resulted in a variability profile that is relatively unrepresentative. We also lack validation of these measurements using independent antibody clones and dyes, or an independent technology such as Cytometry by Time of Flight (CyTOF), and it is likely that some differences represent technical issues rather than biological properties. The major contribution of Tsang and colleagues in this paper is to open up the field of cell-to-cell variation for further investigation, providing a framework for analysis and the software tools required for larger scale comprehensive assessment of the physiological impact of cell-to-cell expression variation.
REFERENCES


