Importance of Protein Variablity In Mammalian Cells.

Dynamic Proteomics of Individual Cancer Cells in Response to a Drug,

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Variability and Robustness in T Cell Activation from Regulated Heterogeneity in Protein Levels

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Recommended with a Commentary by Elisha Moses, Weizmann Institute, Israel

Physicists involved in Systems Biology have been among the first to point out the importance of deviations of individual cells from the average behavior of a culture. Like Physics, Biology includes huge numbers of cells that have an average ensemble behavior, but it contrasts Physics in offering a unique opportunity for individual cells to determine the organism's fate. It may be the rogue cell whose decision to create a tumor eventually kills the organism, or the single immune cell that identifies an invader and recruits the full immune response of the organism.

Elowitz (1) pointed out the large variability in protein production observed in daughter clones of the same *E. coli* bacterium cell. Cluzel (2) then showed that the variability of protein levels in the bacteria impacts on the behavior, or phenotype of the cell. Thus, the same genetic makeup of cells allows for different behavior according to that individual cell's level of expression of proteins. These levels are in turn influenced by both the intrinsic noisiness of the protein production machinery and the extrinsic noise in the fluctuating environment.

Two recent papers now show the importance of the variability in more complex mammalian cells. The group of Alon in the paper highlighted above has performed a *tour de force* in creating a library of over a thousand cell 'lines', based on a human tumor cell. In each cell line, a different gene was forced to accept a fluorescent (GFP) addendum. This allows precise measurements of how many of these proteins are produced, along with a determination of their position in the cell. They then administered the chemotherapy drug for cancer *camptothecin* (CPT) that specifically targets the protein *topoisomerase 1*, associated with DNA replication. They followed the course of the

different protein production, and found while most of the thousand proteins responded strongly, there was little variability between cells for most proteins. Of the thousand proteins, only 24 showed strong variations between cells, and two proteins that battle DNA damage could actually determine whether a cell lives or dies. Thus, variation in the protein production in response to the anticancer drug leads to possible evasion of a cell from cell death.

The work of the Altan-Bonnet group also highlighted above asked how the initial variability in protein levels affects a cell's response to external stimulation. They took immune T cells, for which they had previously established a model describing the role of three central proteins, and measured the relation between the initial abundance of these three proteins and the response to a particular ligand that these cells are attuned to. Here the interesting finding is that the variability in protein levels is what enables a large dynamic response, which is crucial for modulating the organism's response to a variety of insults. Two of the three proteins were predicted to have a high influence, and indeed they functioned as controllers of the response, one as a digital off/on trigger and the other as an analog regulator. They also observed co-variation between these two proteins, which enforces a correlation between them and imposes a constraint on the range of actually available responses. Their conclusion is that flexibility in response is given by proteins that do not obey a type of cell adaptability called robustness. If you are robust to changes in protein levels then you cannot expect to fine tune your behavior by variations on these levels. Noisiness is an inevitable consequence of the microscopic size of cells that causes unreliable behavior, but it also produces heterogeneity on the population level that may actually be harnessed by the population to upgrade their collective performance. Just how this is done still needs to be understood.

References

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