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Immune cells make flexible choices

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Our immune system must be tremendously complex to respond to the unending assault of viruses, bacteria and cancerous cells. One of the mechanisms used by the immune system to cope with the huge variety of possible threats is to randomly combine DNA segments for the production of receptors on lymphocytes – a type of white blood cell. The number of possible receptors that can be produced in this way is about 1000 times the number of stars in our galaxy – one followed by 15 zeroes. And yet, the actual array of receptors produced does not conform to this picture of random chance: Some receptors are produced at a higher rate than others. New research at the Weizmann Institute can help explain how the immune system maintains its complexity while giving preference to certain receptors.

The research team headed by Dr. Nir Friedman, including postdoctoral fellows Drs. Wilfred Ndifon and Hilah Gal, together with Prof. Ruth Arnon and Dr. Rina Aharoni, all of the Immunology Department, looked at the DNA sequences for receptors in immune cells called T lymphocytes. These receptors identify disease agents so they can be destroyed by the immune system. The genetic sequences encoding these receptors are each composed of three random DNA segments – something like the random lineups in a slot machine. Each of those segments is taken from a different area of the lymphocyte cell genome; each area has a full "menu" of segments to choose from. The assembly of the sequence takes place when the DNA strand folds, bringing a segment from the first area close to those in the second and third areas. The sequence is then cut and pasted together, and the excess bits of DNA in between discarded, thus creating a new and unique genetic

sequence for the receptors in each lymphocyte cell.

In a study that appeared recently in the Proceedings of the National Academy of Sciences (*PNAS*), the team used a system they developed based on advanced high-throughput sequencing techniques to investigate the genetic sequences of an entire array of lymphocyte receptors in mice. With this "panoramic view," the researchers were able to assess how widespread each receptor was and even to suggest a reason for the uneven distribution. It appears that the secret is in the pieces of DNA that eventually get discarded: Both the length of these segments and their flexibility – a function of the protein "packaging" that gives them shape – determine how likely it is that two distant segments will meet.

With this insight, the researchers created a model that can predict the production distribution of receptors based on the distance between segments and the flexibility of the DNA. They then looked at small groups of individuals – up to five – to see if they could find common lymphocyte receptor sequences among them. Surprisingly, the team discovered that a group of five was more likely to all share a common sequence than smaller sub-groups. That may seem like saying there is a higher chance of winning at the slot machine five times in a row than twice, but the scientists can explain this finding based on the preferences revealed. The common sequences may simply be situated in the genome in such a way that they are more likely to be integrated into the receptor sequences. Such sequences may have been selected by evolution for their ability to fight common disease agents or prevent autoimmune disease.

Friedman: "While our immune system often seems to rely on 'luck' to produce random receptors against a long list of threats, the shared receptors suggest that this mechanism is finely tuned to ensure a response to common diseases."

More information: www.pnas.org/content/109/39/15865.long

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