Pick me! Pick me! How genes are selected to create diverse immune cell receptors

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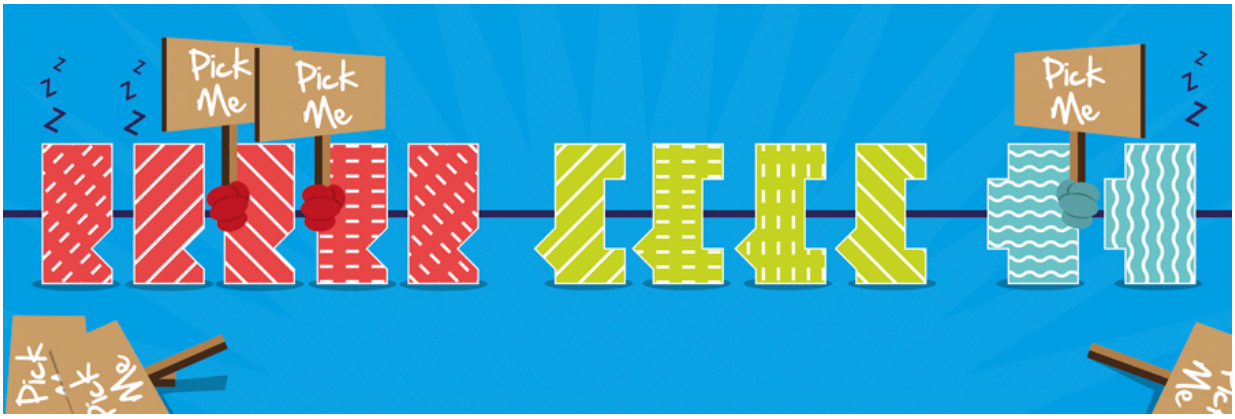

Gene segments with placards have characteristic features that mean they are used frequently, while 'sleeping' gene segments are rarely used. To see this selection in action, see our video presenting the different immune cell types and how they work together. Credit: Babraham Institute

Use of a new technique developed at the Babraham Institute has allowed researchers to take an in-depth look at the gene shuffling process that is responsible for our body's ability to recognise a vast range of foreign agents such as disease-causing microorganisms (pathogens). Failure in this process lies at the heart of a variety of immunodeficiency diseases and is also relevant to the decline in immune function observed with age.

To ensure this diversity, antigen receptors, the cellular receptors that

recognise the presence of pathogens, are assembled from gene segments picked from a wider selection. Every antigen reception is made of a V (variable), D (diversity) and J (joining) region but there are several of each of these regions to choose from. In mice for example, there are 4 J genes, 10 D genes and 195 V genes in the immunoglobulin heavy chain antigen receptor. Mix and matching the regions allows our body to create an enormous range of receptors ensuring that our immune surveillance is equipped to recognise and respond to most pathogens.

How the different V, D and J segments are selected has remained a key question for immunology researchers. A technique developed at the Institute allows the usage of V, D and J segments to be identified by utilising high-throughput sequencing. In research just published in *Cell Reports*, the researchers used the technique, called VDJ-seq, to look particularly at the frequency of use of the 195 V genes in an immune cell type from mice. By using cutting-edge machine learning techniques to integrate this information and the data from genetic and epigenetic analyses, they uncovered the regulatory rules explaining why particular V segments were used or unused.

Dr Daniel Bolland, senior postdoctoral researcher at the Babraham Institute and co-first author on the paper, said: "The selection of the different gene segments to create a receptor is not random. Our research showed that there is a wide range in frequency with which a particular V gene segment is utilised. This points to the involvement of complex regulatory mechanisms and our findings contribute towards establishing what these are and how they influence the selection." Dr Hashem Koohy, also a postdoctoral researcher at the Babraham Institute and co-first author on the paper, added: "Integrating the frequency of selection of different V segments with information on other factors also playing a role in recombination efficiency allowed us to establish the pattern of features that are associated with active V segment usage."

Dr Mikhail Spivakov, group leader in the Nuclear Dynamics research programme and co-corresponding author, commented: "This is an exciting example of powerful synergy between experimental and computational approaches."

Dr Anne Corcoran, research group leader in the Institute's Nuclear Dynamics programme and co-corresponding author, said: "Understanding the VDJ recombination process is important because it is the first determinant of receptor diversity. Having a precise readout of which V, D and J segments are used advances our understanding of the process of recombination and how this is regulated. These finding have implications for immune disorders and aberrant VDJ recombination in cancer."

More information: Bolland and Koohy et al. (2016) Two mutually exclusive local chromatin states drive efficient V(D)J recombination, *Cell Reports*, DOI: 10.1016/j.celrep.2016.05.020 , www.cell.com/cell-reports/fulltext/S2211-1247%2816%2930588-5

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