How new loops in DNA packaging help us make diverse antibodies

September 13 2019

Diversity is good, especially when it comes to antibodies. It's long been known that a gene assembly process called V(D)J recombination allows our immune system to mix and match bits of genetic code, generating new antibodies to conquer newly encountered threats. But how these gene segments come together to be spliced has been a mystery. A new study in *Scientific Reports* provides the answer.

Our DNA strands are organized, together with certain proteins, into a packaging called chromatin, which contains multiple loops. When a cell needs to build a particular protein, the chromatin loops bring two relatively distant DNA segments in close proximity so they can work together. Many of these loops are fixed in place, but cells can sometimes rearrange loops or make new loops when they need to—notably, cancer cells and immune cells.

The new research, led by Frederick Alt, Ph.D., director of the Program in Cellular and Molecular Medicine (PCMM) at Boston Children's Hospital, shows in exquisite detail how our immune system's B cells exploit the loop formation process for the purpose of making new kinds of antibodies.

Scanning loops as they form

A pair of enzymes called RAG1 and RAG2, the researchers show, couple with mechanisms involved in making the chromatin loops to

initiate the first step of V(D)J recombination—joining the D and J segments. The RAG 1/2 complex first binds to a site on an antibody gene known as the "recombination center." As the DNA scrolls past during the process of loop formation ("extrusion"), the RAG complex scans for the D and J segments the cell wants to combine. Other factors then impede the extrusion process, pausing the scrolling DNA at the recombination center so that RAG can access the desired segments.

"The loop extrusion process is harnessed by antibody gene loci to properly present substrate gene segments to the RAG complex for V(D)J recombination," says Alt.

While many of the hard-wired chromatin loops are formed and anchored by a factor known as CTCF, the Alt lab shows that other factors are involved in dynamic situations, like antibody formation, that require new loops on the fly. The study also establishes the role of a protein called cohesin in driving the loop extrusion/RAG scanning process.

"While these findings have been made in the context of V(D)J recombination in antibody formation, they have implications for processes that could be involved in gene regulation more generally," says Alt.

More information: Ke Li et al, Preoperative Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio are Associated with the Prognosis of Group 3 and Group 4 Medulloblastoma, *Scientific Reports* (2019). DOI: 10.1038/s41598-019-49733-6

Provided by Children's Hospital Boston