Understanding epigenetic control of antibody responses

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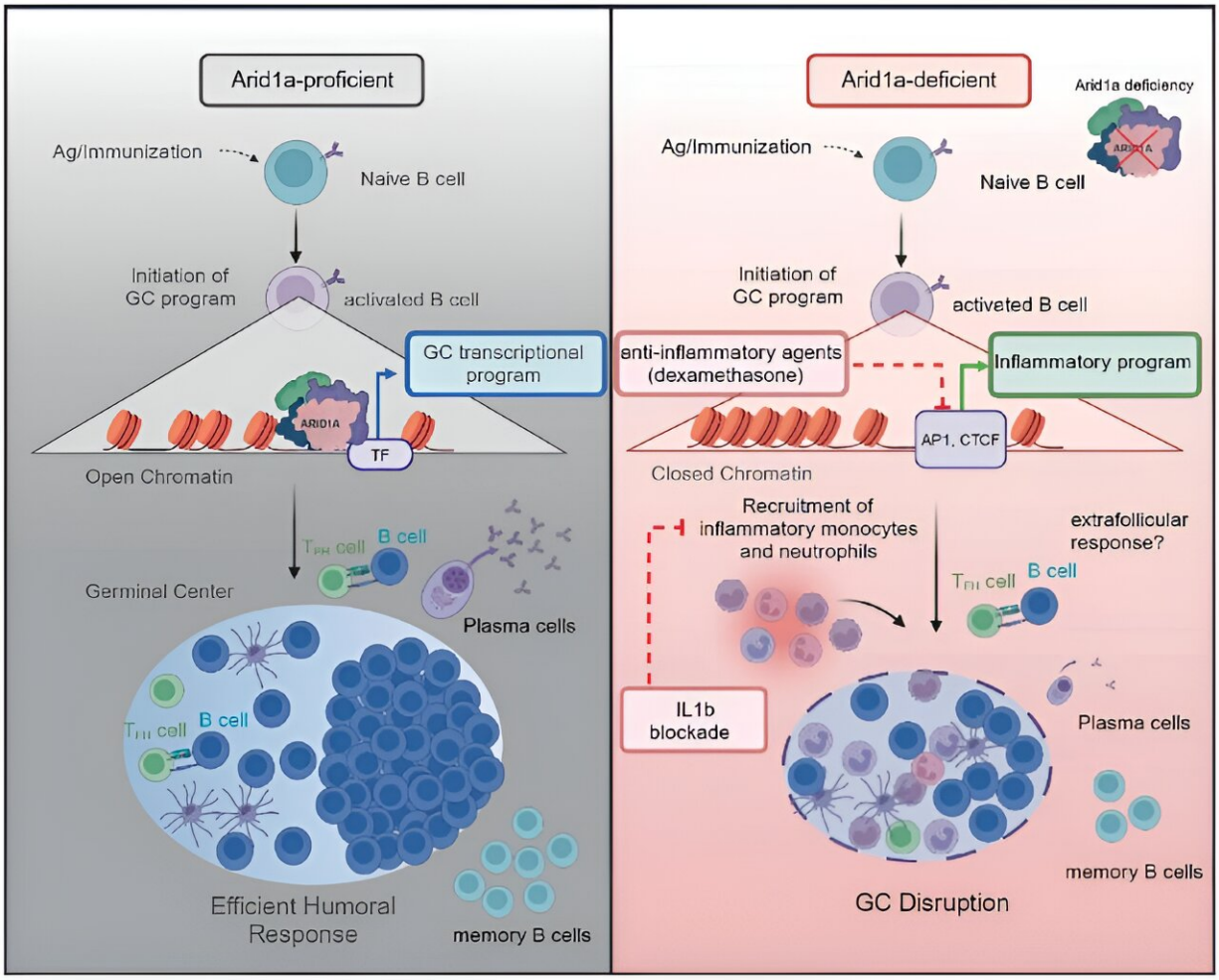

Proposed model by which Arid1a regulates GC responses. On left, Arid1a mediates the establishment of chromatin landscapes required for GC transcriptional program. On right, Arid1a deficiency instigates an inflammatory transcriptional program which recruits inflammatory cell types leading to

premature GC collapse. Credit: *Nature Immunology* (2024). DOI: 10.1038/s41590-024-01920-y

Northwestern Medicine investigators have uncovered how antibody responses are regulated by epigenetic factors commonly mutated in cancers, according to a study published in *Nature Immunology*.

Mammalian Brg1/Brm-associated factor, or BAF, complexes are highly mutated in several types of cancer, and their role in normal cellular physiology continues to be an active area of investigation, said Vipul Shukla, Ph.D., assistant professor of Cell and Developmental Biology, who was senior author of the study.

"The BAF complexes are known to be important for development in mammals, and are also frequently mutated in cancers, including cancers that originate from B lymphocytes, which are antibody-producing cells in our body," said Shukla, who is also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

In the study, Shukla and his colleagues set out to understand how BAF complexes contribute to the physiology and function of B lymphocytes.

To better understand how the complexes affect immune responses, investigators studied mice with genetic deletion of the BAF complex. They found that the gene Arid1a, which is an essential subunit of the mammalian BAF complex, is pivotal for the normal functioning of B lymphocytes.

Additionally, B lymphocytes lacking Arid1a exhibited molecular signatures associated with the activation of inflammatory genes, which disrupted normal immune responses.

"The turning on of inflammatory signatures in the absence of Arid1a was a really surprising finding, considering that the BAF complexes are primarily known to turn on and not turn off gene expression," said Daniela Samaniego-Castruita, Ph.D., a postdoctoral student in the Shukla lab and a co-first author of the paper.

"In the absence of this complex, inflammatory myeloid cells, which are typically not found in secondary lymphoid tissues, begin to accumulate at these sites and lead to disruption of immune responses," said Ajay Abraham, Ph.D., a member of the Shukla lab and co-first author of the study.

Next, investigators attempted to dampen inflammatory responses in mice missing Arid1a. To do this, they used two distinct approaches: they inhibited IL1b, a protein known to kick off inflammation in the body, and treated mice with Dexamethasone, a well-known anti-inflammatory corticosteroid. Upon inhibition of IL1b or treatment with Dexamethasone, the scientists observed that mice lacking Arid1a in B-cells partially returned to generating normal antibody responses, according to the study.

"One of the most important findings from our study was the fact that uncontrolled inflammation can have paradoxical effects on inhibiting adaptive immune responses," Shukla said. "These findings attest and add to an emerging conceptual paradigm in immunity, which highlights that unrestricted inflammation could dictate the quality of the adaptive immune response."

Such a mechanism might be central to preventing autoimmunity, he said.

These findings show how BAF complexes function to regulate immune responses and may provide insights into how modulating inflammatory responses could be useful in treating cancers with BAF complex

mutation, Shukla said. Shukla's lab will continue to study how BAF impacts inflammatory responses and alters the immune landscape.

"Our lab started at Northwestern just two years ago, and this work would not have been possible without the amazing research support and mentoring environment available to junior faculties at Northwestern," Shukla said.

More information: Ajay Abraham et al, Arid1a-dependent canonical BAF complex suppresses inflammatory programs to drive efficient germinal center B cell responses, *Nature Immunology* (2024). DOI: 10.1038/s41590-024-01920-y

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