For lupus patients, anti-inflammatory immune cells are maturing Into wrong cell type

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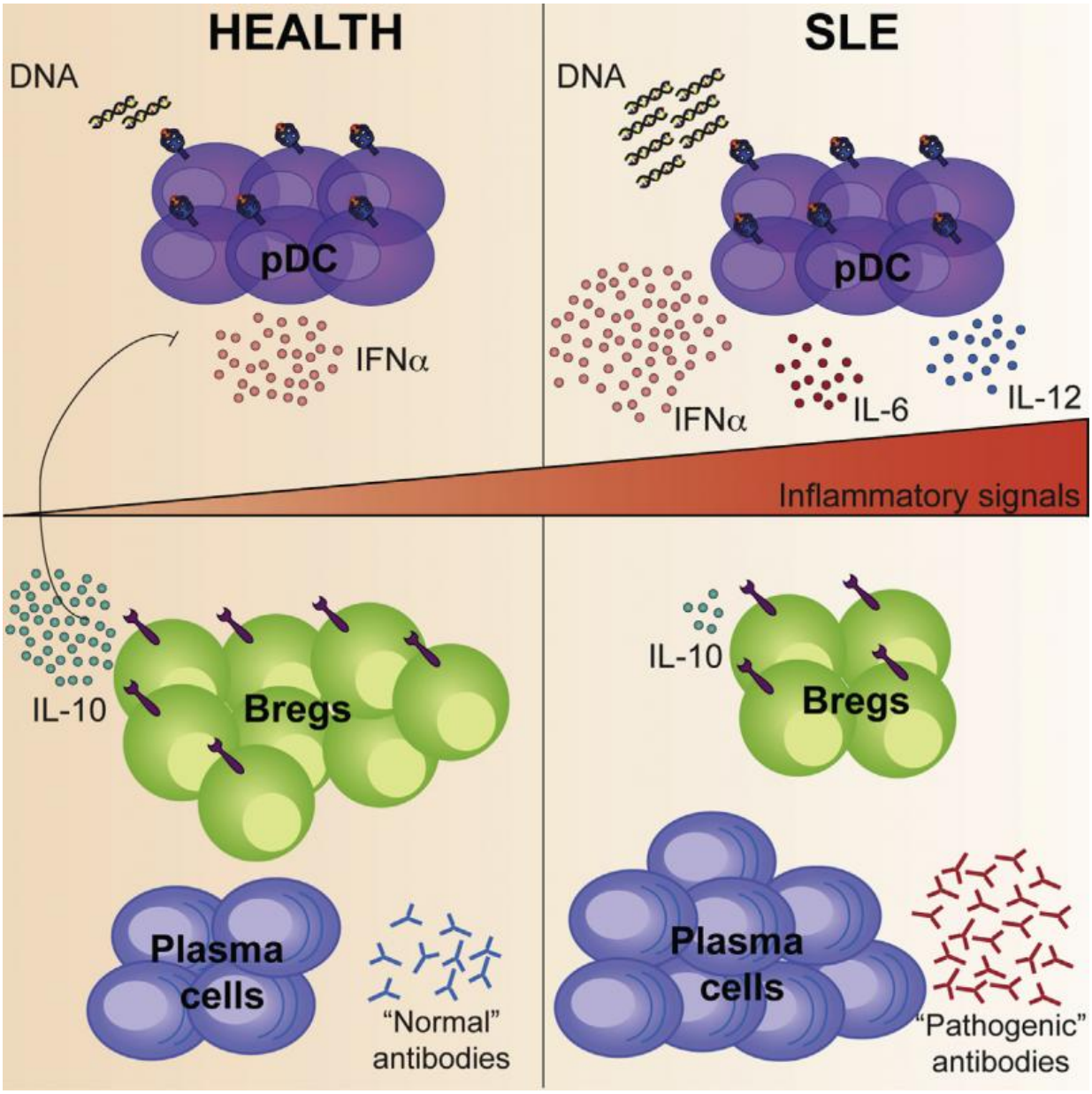

The signals required for Breg cell differentiation in humans are currently unknown. This visual abstract depicts what Mauri and colleagues show, that plasmacytoid dendritic cells, via the provision of IFN-a, govern the differentiation of immature B cells into regulatory B cells that restrain inflammation. Credit: Menon et al./*Immunity* 2016

One of the mysteries of lupus is why the immune cells that normally keep inflammation at bay can't seem to do their job. A University College London study published on March 8 in *Immunity* now suggests that for people with lupus, the B cells that regulate inflammation are getting signaled to become pro-inflammatory cells instead. The research, done using human blood samples and genetic profiles, also provides evidence that how a lupus patient responds to treatment is related to their levels of these cellular signals.

This miscommunication in lupus patients seems to come from an imbalance of three types of immune cells: B cells that produce antibodies to protect the body against foreign microbes (and a main driver of autoimmune disorders); plasmacytoid dendritic cells that produce a molecular signal called interferon-alpha (IFN-α) that stimulates B cells; and regulatory B cells that suppress excessive immune responses, which come in short supply for lupus patients.

"Our study shows for the first time that the overproduction of IFN-α by hyperactivated plasmacytoid dendritic cells in lupus patients is the consequence of the lack of suppressive regulatory B cells," says senior author Claudia Mauri, an immunologist at University College London. "The uncontrolled production of IFN-α causes an increase of antibody-producing B cells and suppresses the division and appearance of

regulatory B cells."

The researchers also discovered a potential reason why rituximab, a drug that has been used off-label to treat lupus by depleting the vast majority of circulating B cells, benefits some patients with lupus but not others. The data come from analyzing immune cells and genetic activity from nearly 100 healthy volunteers and 200 people with lupus.

"After treatment, newly formed B cells come back into circulation," says lead author Madhvi Menon, a postdoctoral researcher in Mauri's lab. "Our study suggests that response to rituximab is determined by the presence or absence of an elevated IFN-α-related gene activity," she says. "Thus, only in patients that have a normal IFN-α signature do the newly repopulated B cells successfully mature into regulatory B cells."

The results suggest that lupus patients should be tested for this IFN-α-related gene signature prior to treatment with rituximab. "This would be an important step towards personalised medicine for the treatment of lupus," Mauri says.

More information: *Immunity*, Menon et al.: "A Regulatory Feedback between Plasmacytoid Dendritic Cells and Regulatory B Cells Is Aberrant in Systemic Lupus Erythematosus"
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