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Flick of a protein switches immune response

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A single protein can turn on and off a key component of the immune system by changing partners in an elegant genomic dance, said researchers at the University of Southern California and Harvard Medical School.

Because autoimmune diseases – such as arthritis, allergies and dozens of other illnesses – begin when the body's defenses respond at the wrong time or place, the on-off mechanism for the immune system has been the subject of intense study for decades.

The USC-Harvard team studied proteins critical to immune tolerance, a term for the healthy balance between a weak immune system and an overly aggressive, indiscriminate watchdog.

Lin Chen, professor of molecular and computational biology at USC and lead co-author with Harvard's Anjana Rao, said the team's result would "open a big door for people to explain the fundamental mechanism of immune tolerance."

In the July 28 issue of *Cell*, the USC-Harvard group shows that the protein Nuclear Factor of Activated T cells (NFAT), in collaboration with FOXP3, an essential factor in regulatory T cells, orchestrates a genetic program critical to immune tolerance.

But the same NFAT, paired with a second family of proteins known as AP-1, instead stimulates immune response.

Chen said the finding offers the first strong evidence in favor of the 15-year-old "combinatorial control" theory of gene expression.

According to the theory, the specific expression of a gene depends on the combination of "transcription factors" acting on it. Transcription factors help to translate a gene's instructions into actual proteins. FOXP3 and NFAT are two such factors; the human body contains around 3,000.

"The work provides a structural demonstration of combinatorial control of gene expression," Chen said. "This is, in my view, the most direct demonstration that this is indeed happening in nature."

The researchers were able to identify single genes that were activated by NFAT in combination with AP-1 and suppressed by NFAT with FOXP3.

Beyond shedding light on the immune system, the Cell paper may advance biology and medicine toward a much larger goal: how to turn single genes on or off.

"This [result] has far-reaching implications for understanding the principles of signal transduction and transcriptional networks of living cells," Chen said.

The Cell paper, which Chen describes as spanning 14 years of laboratory work, builds on a result his group published in *Nature* in 1998.

Source: University of Southern California