Why do people respond differently to the same drug?

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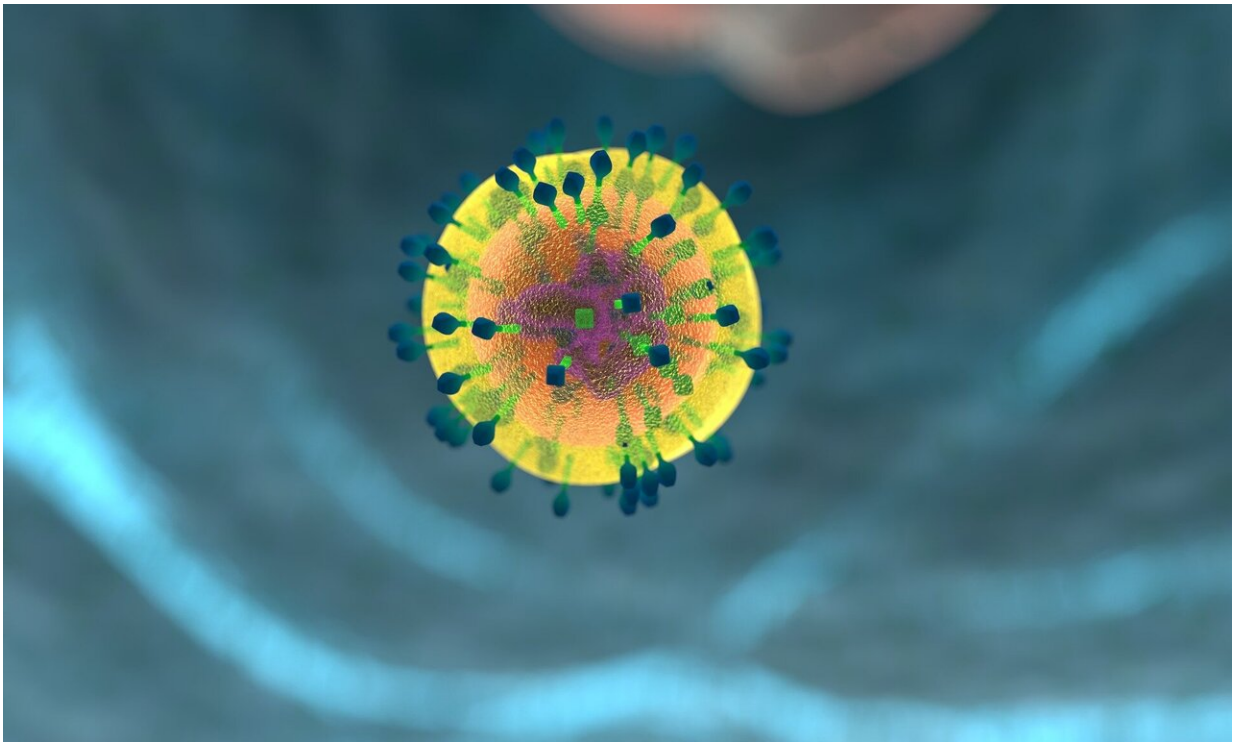

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Scientists at Scripps Research have comprehensively mapped how a key class of proteins within cells regulates signals coming in from cell surface receptors.

The study reveals, among other things, that people commonly have

variants in these proteins that cause their cells to respond differently when the same cell receptor is stimulated—offering a plausible explanation for why people's responses to the same drugs can vary widely.

The findings, published October 1 in *Cell*, set the stage for a better understanding of the complex roles these proteins, known as RGS proteins, play in health and disease. That in turn could lead to new treatment approaches for a range of conditions.

"Before you can fix things, you need to know how they're broken and how they work normally, and in this study that's essentially what we've done for these important regulatory proteins," says study senior author Kirill Martemyanov, Ph.D., professor and chair of the Department of Neuroscience at Scripps Research's Florida campus.

A reset button for cell receptors

RGS proteins, discovered about 25 years ago, provide an essential "braking" function for a large family of cellular receptors called G-protein-coupled receptors. GPCRs, as they're known, control hundreds of important functions on cells throughout the body, and have been implicated in dozens of diseases, from heart problems to vision impairments and mood disorders. Accordingly, GPCRs comprise the largest single category of drug targets—more than a third of FDA-approved drugs treat diseases by binding to GPCRs and modifying their activities.

When GPCRs are activated by hormones or neurotransmitters, they initiate signaling cascades within their host cells, via signal-carrying proteins called G-proteins. RGS (Regulator of G-Protein Signaling) proteins work by deactivating G-proteins, shutting off this signaling cascade. This shutoff mechanism limits G-protein signaling to a brief

time window and allows cells to reset and accept new incoming signals. Without it, the GPCR-initiated signal stays on inappropriately and functional signaling becomes dysfunctional.

"One condition I studied earlier in my career involves the loss of RGS regulation in light-detecting cells in the retina," Martemyanov says. "Patients born with this condition can't stop perceiving light, even when they go into a dark room, and they can't track moving objects very well because they lack the normal visual refresh rate. It's easy to imagine how devastating it would be if you had a similar loss of RGS regulation in the heart or the brain where timing is so important."

Scanning the 'barcodes' for clues

Researchers have evaluated some RGS proteins individually, but in the new study, Martemyanov and colleagues painstakingly covered all 20 of the RGS proteins found in human cells, studying how each one selectively recognizes and regulates its G-protein counterparts. In so doing the researchers essentially created a roadmap for how GPCR signals are routed in cells.

"This selective recognition of G-protein subunits turns out to be performed by a few elements in each RGS protein—elements organized in a pattern resembling a barcode," says study first author Ikuo Masuho, Ph.D., staff scientist in the Martemyanov lab.

In an analysis of the genomes of more than 100,000 people, the researchers showed in general how mutations and common variations in RGS barcode regions can disrupt RGS proteins' recognition of G-proteins or even cause them to recognize the wrong G-proteins. The team also demonstrated a particular example, showing how mutations in the RGS protein known as RGS16, which have been linked to insomnia, cause it to lose its usual recognition of G proteins.

"It's clear that genetic variation in the RGS barcode regions has the potential to disrupt normal GPCR signaling, to cause disease or to create more subtle differences or traits," Martemyanov says. "For example, it may help explain why different individuals treated with the same GPCR-targeting drug often differ widely in their responses."

Martemyanov and his team found that RGS proteins' barcode regions and the G-proteins they regulate are constantly evolving. They were able to reconstruct less refined, "ancestral" RGS proteins, based on analyses of different species. From these findings they were able to devise principles for crafting "designer" RGS proteins that regulate a desired set of G-proteins.

The same principles could guide the development of drugs targeting RGS proteins for therapeutic benefits, a major ongoing effort in the GPCR field. Treatments that put corrective new RGS proteins in cells might be another avenue, Martemyanov says.

More information: Ikuo Masuho et al, A Global Map of G Protein Signaling Regulation by RGS Proteins, *Cell* (2020). DOI: 10.1016/j.cell.2020.08.052

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