Q&A: Gordon Mills on Neomorphs in Cancer

Identifying and characterizing gain-of-novel-function aberrations are key in rational drug design

Genomic aberrations in cancer are often classified as hypomorphic, such as the inactivation of tumor suppressors, or hypermorphic, such as the activation of oncogenes. However, Gordon Mills, MD, PhD, chair of systems biology at The University of Texas MD Anderson Cancer Center in Houston, says a third category merits attention: neomorphs, gain-of-novel-function mutations that "rewire a protein's function so it links to pathways and events that the parental molecule does not." Mills discussed how neomorphs are characterized and their therapeutic ramifications in this era of precision medicine with *Cancer Discovery*'s Alissa Poh.

Neomorphs aren't yet widely appreciated. What do your peers think?

Most agree this is an incredibly important concept. A handful have questioned my point, saying *all* mutations are essentially neomorphic, because each one results in changes to cellular signaling. However, I'm talking about *unexpected* rewiring that can't be predicted, at least not based on our understanding of the parent molecule's canonical function.

For instance, my lab was screening *PIK3R1* mutations against a large series of drugs, looking for therapeutic susceptibilities. We saw, unexpectedly, that a particular mutation rendered cells sensitive to multiple inhibitors of MEK and JNK. We determined that it turns on elements of RAS–MAPK signaling and is neomorphic. We'd have missed this if we employed the "streetlight approach" and focused only on increased sensitivity to AKT inhibition—the canonical PI3K pathway.

So neomorphs are clinically important?

Yes. The *PIK3R1* neomorph we found uses a different, unpredicted pathway, so targeting PI3K signaling wouldn't produce the hoped-for therapeutic response. It might even exacerbate aberrant MAPK activity, although this possibility is just conceptual. We don't have proof that it happens.

What's another example of a neomorphic aberration?

IDH1/2 mutations have been reported in gliomas and acute myeloid leukemia (AML), among other cancers. Normally, both isoforms catalyze the conversion of isocitrate to α-ketoglutarate. *IDH1/2* mutations, however, result in 2-hydroxyglutarate being produced from α-ketoglutarate. Because 2-HG is structurally similar to α-KG, it functions as a competitive inhibitor of α-KG–dependent enzymes downstream. The two products have diametrically opposed effects on cellular function—mutant *IDH1/2*'s neomorphic effects have completely rewired the network regulated by these enzymes.

Can neomorphs arise from mechanisms other than point mutations?

There are numerous reasons why a mutation may be neomorphic. Our *PIK3R1* neomorph is the result of a stop codon gain. *BCR–ABL* is widely considered a hypermorph, but I think it's a neomorph. I'd argue its function couldn't have been predicted from what we knew of either protein alone—the gene fusion alters the location of ABL's activity, which changes the functional consequences, because it now has different partners. Insertions or deletions that change a molecule's structure will change its binding partners.

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To move ahead with precision medicine, understanding gain-of-novel-function mutations could be critical in devising effective treatments for individual patients, says Gordon Mills, MD, PhD.

How are neomorphs discovered and characterized?

In many cases, they're found by looking at the expected results of saying, "This is a simple hypermorph," but seeing that these results fail to explain what's actually observed in terms of functional consequences.

At MD Anderson's Khalifa Institute for Personalized Cancer Therapy, which I codirect, and through the NCI's Cancer Target Discovery and Development program, we've started functionally characterizing mutations in patients to determine if these are drivers or passengers. By using reverse-phase protein arrays, RNA sequencing, informer drug libraries, and metabolomics, we've built a pathway-agnostic platform that allows us to see unexpected neomorphic effects more easily. I think these new transcriptome- and proteome-probing technologies will demonstrate that many mutations in patients have functional consequences we wouldn't have anticipated.

Can neomorphs be predicted?

A group in Denmark has developed a computational algorithm, ReKINect, to look for mutations that perturb signaling networks by altering phosphorylation sites and pH domain function, and are therefore neomorphs. They were able to identify and validate a few. However, for many aberrations, if not most, I think functional probing will be necessary to determine neomorphic effects.

How might neomorphs be therapeutically targeted?

Inhibitors specific to mutant *IDH1/2* are showing encouraging activity in patients with AML. Regarding the *PIK3R1* neomorph, dual MAPK and PI3K blockade has produced enhanced antitumor effects in cell lines and mice, and is being explored in the clinic. Various neomorphs are being investigated, but there isn't enough patient data other than to say that clinical trials are under way.

The point to emphasize is this: As we characterize genomic aberrations in greater detail, we'll likely find more that can be classified as rewiring, not merely increasing or halting, the parental molecule's function, in unexpected ways. Understanding this is key as we move ahead with precision medicine, or we could miss changes that may have therapeutic ramifications. ■

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