Chromosomal translocations point the way toward personalized cancer care

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A broken chromosome is like an unmoored beansprout circling in search of attachment. If a cell tries to replicate itself with broken chromosomes, the cell will be killed and so it would very much like to find its lost end. Often, it finds a workable substitute: another nearby chromosome. When a broken chromosome attaches to another, or when chromosomes use a similar process to exchange genetic material, you've got a translocation – genes end up fused to other genes, encoding a new protein they shouldn't. A recent University of Colorado Cancer Center review in the journal *Frontiers of Medicine* shows that you also frequently have the cause of cancer – and in some cases its cure.

"The most famous example is the Philadelphia chromosome – the translocation and fusion of genes BCR and ABL that causes chronic myeloid leukemia," says Jing Wang, MD, PhD, University of Colorado Cancer Center investigator and assistant professor of immunology at the CU School of Medicine, the review's author.

Other oncogenic translocations include the fusion of genes ALK and EML4 to create what's known as ALK+ non-small cell lung cancer.

The promise of recognizing these cancer-causing translocations is the potential to target cells with these genetic mutations. Find a therapy that seeks and destroys a specific translocation or cells that have learned to depend on a translocation for survival and/or growth, and you can kill cancer without killing surrounding, healthy cells. In a nutshell, that's the goal of targeted cancer therapy – the current revolution underway in

cancer research to selectively target cancer cells.

"Since their discovery, chromosomal translocations have made a critical impact on diagnosis, prognosis and treatment of cancers," Wang writes.

In CML, the revolutionary drug Gleevec targets the energy mechanism of cells with the Philadelphia chromosome; in ALK+ lung cancer, the drug crizotinib, developed largely at the CU Cancer Center, targets the energy system of these cells. In both cases, targeted therapies kill cancerous cells with these translocations while leaving healthy cells unharmed. Recognizing specific translocations can also allow doctors to offer a more accurate prognosis and may inform treatment decisions.

Still, "there are many challenges in this developing science," Wang says. "The first is describing the mechanism of these translocations, for example, whether chromosomes that are near each other are prone to joining in ways that allow them to exchange or fuse genetic material, or if chromosomes that spontaneously break then go looking around for partners." There are scientists on either side of this breakage first or contact first hypothesis.

Another challenge is discovering which translocations cause cancer and which just happen to hitchhike along with other mutations that are cancer's true cause.

"From human tumors, you can get frequency data," Wang says – you can discover what translocations are frequent in types of cancer. "But this is correlative. To discover if a translocation is oncogenic, you need other models."

New technologies including next-gen DNA sequencing make it increasingly easy to discover the genetic differences between cancerous and healthy cells. "In 20 years we're talking about personalizing the

genome," Wang says, meaning that every individual cancer patient could be genetically screened for every genetic mutation and then treatment based on the signature of their mutations.

But discovering which mutations matter is another story. When you pinpoint a mutation, for obvious reasons you can't create a translocation in a human and then watch to see if cancer develops. And so the process of vetting thousands of translocations for their oncogenic power is tedious and involved.

Even once you discover an oncogenic translocation, it remains unsure whether the discovery will prove therapeutically useful. "Sometimes even when we know a translocation is important, we might not be able to do anything about it," Wang says. "Sometimes these translocations might be present in healthy cells that we don't want to kill or some genes involved in translocations may be essential factors for cell survival. For example, we know that c-myc gene is upregulated in specific type of lymphomas but targeting c-myc gene will result in very high toxicity. Or in still other cases drugging the target can be more difficult than in others."

Today's challenge may be tomorrow's cure. Right now we're in the midst of a cancer care revolution toward personalized care based on a cancer's genetic signature – and the study and exploitation of chromosomal translocations may lead the way.

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