Q&A: Elizabeth Blackburn on Telomerase and Tumors

Studies advance knowledge of telomere maintenance in cancer and in healthy immune systems

"More and more of us are thinking that the way we really get rid of this problem of resistance to targeted cancer drugs is to actually kill the cells, as opposed to throttling them down," says Elizabeth Blackburn, PhD, professor of biology and physiology at the University of California, San Francisco, and a 2009 Nobel laureate. “From that point of view, there’s a lot of life in research on interfering with telomeres.” Blackburn discussed research on these regions of repetitive DNA at chromosome ends, and related strategies to treat or delay cancer, with Cancer Discovery’s Eric Bender.

How did research start on cancers and telomere biology?

It’s very clear that telomere biology and telomerase are very intimately related to the cancer cell and often to whether cells will survive or not. The simple idea years ago was that normal cells don’t have much telomerase in adults and cancer cells have very high levels. That observation is true in a general sense, but it’s more complicated than people thought. Stem cells and hematopoietic cells that have to keep functioning through life do have telomerase, and you can’t just hit all the telomerase on the head with an inhibitor without getting side effects.

Can you give a few examples of what we’re learning now?

One comes from a very interesting series of papers that came out this year and highlighted the incredible importance of telomeres and telomerase in cancers. Two papers in Science showed that mutations in the promoter region of the TERT gene (which encodes the catalytic subunit of telomerase) that increased TERT transcription by only twofold or less were the most prevalent mutations in the genome for melanomas [Science 2013;339:957–9 and 959–61]. Then another group found that the same kinds of mutations also were the most prevalent mutations in gliomas and several other cancers [PNAS 2013;110:6021–6]. These groups weren’t looking for TERT mutations; the results just jumped out. The effect is really powerful.

Another is from our own work. There is a form of the TERT protein that is very highly expressed in many cancers, but, guess what, it actually lacks the reverse transcriptase domain. So this protein absolutely cannot be a telomerase enzyme. Why would cancer cells express such a thing? Well, it turns out that this protein is protective against certain kinds of induced apoptosis [Cancer Res 2013;73:2817–28].

What advances are we seeing in telomerase inhibition?

There’s a lot of discussion about combination therapies, in which it’s probably important to kill the cells and not just slow them down. In a few cases of combining a telomerase inhibitor with clinical cytotoxic drugs, you get synergistic killing. This might revive some uses of telomerase inhibition of cancers, although it is early stages.

For telomerase inhibitors themselves, the main progress is about whether there’s a therapeutic window. Initially people thought if you had telomerase inhibition, you’d have to run down the telomerase for a long time. But it now seems that if one can make the cancer cells much more vulnerable to the lower telomerase, in combination with other drugs, one won’t have to wait that long.

There are many ways to interfere with telomerase. One that we took a few years ago was to introduce a telomerase RNA that makes “toxic telomeres.” Telomerase RNA is part of the enzyme, and the RNA has a template which telomerase uses to copy the correct telomere sequence onto the end of the chromosome. If you add the wrong sequence, the cell just commits suicide. So it’s a good cell killer and it’s pretty fast. If there’s a therapeutic window, you could get in and kill the cells very quickly, and then you wouldn’t have to treat the cells for very long periods. The technologies for targeting agents to cancer cells and for introducing nucleic acids into cells are getting much better all the time, so this might be an approach that one could dust off.

You also look at telomeres in preventing or delaying disease?

Yes, good telomere maintenance is very clearly both correlative and causally involved in having a good, functional, noninflammatory immune system, which is more and more tied into the overall picture of what keeps cancers under control. We and our collaborators look at observational clinical studies, which are getting very strong. They give you every reason to say that everything your mother told you about exercise and eating moderately and sleeping well can be related to telomere maintenance, particularly maintenance of the immune system, and, in turn, to disease. Now the challenge is to go beyond the little pilot intervention studies into much more full-fl edged studies, and see what interventions quantitatively do.

Interventions that reduce people’s chronic stress, which is one way to improve telomere maintenance, are starting to play out in cancer survivors. In one study of 464 bladder cancer patients, for instance, the presence of short blood-cell telomeres by itself was not a very strong predictor of mortality, but it had a very synergistic association with symptoms of depression, with the combination increasing risk of mortality threefold. So to improve the chances of being able to take advantage of the ever-improving cancer therapeutics, you can treat for depression and try to do the sorts of things that at least in observational studies have improved telomere maintenance of the immune system.
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