Science Translational Medicine Podcast

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Host – Angela Colmone
Hello, I'm Angela Colmone. Welcome to the *Science Translational Medicine* Podcast for March 23rd, 2011. In this show, I will be speaking with Dr. Timothy Chan of the Memorial Sloan-Kettering Cancer Center about a new way to predict breast cancer metastasis.

Breast cancer is the most common invasive cancer in women, and survival rates vary greatly depending on at what stage the cancer is detected. Women diagnosed with stage 4, or metastatic, breast cancer have only a 10% survival rate, even with aggressive chemotherapy and radiation treatment. Diagnosing breast cancer as early as possible and identifying which cancers are likely to spread is key to beating this disease. Timothy Chan and his team now use the power of genomics to identify a special methylation signature in breast cancer DNA that can indicate the metastatic potential of the cancer.

Interviewer – Angela Colmone
Here now is Timothy Chan on the line to tell us more. Welcome, Dr. Chan, and thank you for joining us.

Interviewee – Timothy Chan
Great. Thanks very much, Angela, and thanks to *Science Translational Medicine* for having me on today.

Interviewer – Angela Colmone
What is a methylome, and what made you decide to look at this feature of breast cancer DNA?

Interviewee – Timothy Chan
Well, so first of all how instructions are encoded by DNA and is carried out by the cell is dictated by both the DNA sequence of the bases, as well as the non–base pair changes to the DNA. And these non–base pair changes of DNA include the DNA methylation changes that we studied, as well as changes to chromatin, and combined these are called epigenetic changes. And these are exceptionally powerful changes and, as you know, the DNA sequence between a human's skin cell and a brain cell and, you know, even more dramatically between say a queen bee and a worker bee is identical, but the epigenetic changes, like DNA methylation, are the key components that are responsible for the dramatic variation in how cells and tissues work. And so, the methylome is really what is

termed the genome-wide pattern of DNA methylation that occurs in cells—in the genome of cells—and it actually dictates both genomic structure and, in part, what genes are expressed and silenced in different types of tissues. And so, one of the questions in cancer research currently that is unknown are really what the root causes of metastasis. And what we studied in our paper that's coming out in *Science Translational Medicine* is how the methylome—or the genome-wide changes in methylation—affect the process of metastasis.

Interviewer – Angela Colmone
So, how did you go about detecting the breast cancer methylome?

Interviewee – Timothy Chan
Well, to study the methylation changes we utilized some new techniques that were developed and engineered by Illumina, and these are essentially whole genome-wide microarrays. And we use these and coupled the analysis of the DNA methylome with standard mRNA expression arrays, and we were able to identify widespread changes and deregulation in the DNA methylome using these microarrays. We then actually optimized the signature of the methylome in the specific subsets of breast cancers using mass spectrometry and developed a clinical test that we used to validate our findings in the largest set of cancers.

Interviewer – Angela Colmone
What clues made you realize that the breast cancer methylome and metastatic potential might be linked?

Interviewee – Timothy Chan
Well, this actually goes back several years now. And, in the last several years, whole exome sequencing and whole genome sequencing has now been completed for matched pairs of breast cancer primaries in metastatic tumors, and this has been done by several labs, including Elaine Mardis' lab, as well as our lab. And what we found was very surprising, actually, that there are actually very few metastatic-specific alterations that have been found—in other words changes in the DNA sequence that are only found in metastasis specific for that last event of cancer progression, the development of distant lesions. And that coupled with the idea that we have known for a while that the process of metastasis involves developmentally regulated processes, such as epithelial to mesenchymal transition with a loss of these terminally differentiated states in epithelial cells. And this combination of ideas led us to the hypothesis, which is the basis of the course of research that we described in our upcoming paper, which is that normal breast cancer cells have lost this ability to maintain a developmentally regulated state. And we know that these types of developmental processes are closely tied with DNA methylations—it was a natural course to go ahead and study alterations in DNA methylation on the genome-wide scale as a basis for metastasis.

Interviewer – Angela Colmone
So does this methylome signature apply to other types of cancer, as well?

Interviewee – Timothy Chan
Yes, so we actually compared, in our paper, the breast cancer CIMP genes to methylation patterns in glioma and colon cancer. And it turns out, strikingly, that there is a similar hypermethylation dysfunction in not only breast cancer but glioma and colon cancer. And intriguingly the presence of this CIMP phenotype predicts good prognosis in all three types of cancers—GBM, breast cancer, and colon cancer. And so, what we actually hypothesized is that we're looking at a fundamental force of tumorigenesis—much like genetic instability, but in our case we're looking at methylome instability, in that this methylome deregulation may actually be in the beginning helping to promote oncogenesis, but paradoxically later on silence genes because of the same mechanisms of silencing acting on different types of genes. But, these genes may, in fact, later on be required for metastasis. So, you know, I think that this methylome deregulation may not necessarily be the case in the CIMP-negative tumors, which are genetically unstable and may use chromosomal instability as a mechanism to driving tumorigenesis. So, I think what we're looking at is two very different types of cancers and, you know, in addition to breast cancer this may have bearings on a variety of different human malignancies.

Interviewer – Angela Colmone
How will detecting the breast cancers most likely to metastasize affect patient care?

Interviewee – Timothy Chan
I think right now in the treatment of different types of cancers, including breast cancer, this represents one of the most important aspects of oncology, and that is how to really, really accurately determine those patients who are at metastatic risk. And this is partly what our paper also addressed, in that our tests, I think, can be used alone or in conjunction to develop the better clinical tests for breast cancer patients. And, you know, ultimately—to answer you question—by identifying which patients which are at the highest risk for metastases, we're able to determine which patients need more aggressive therapies and which patients may not necessarily need chemotherapy or systemic therapies. They may be spared the toxicities of chemotherapy. And this is very important because some of these more aggressive patients may ultimately be the ones that we want to put on trials—these are the ones where standard therapies don't necessarily do a good job at helping patients beat the disease. So, you know, it's our hope that the analyses that we've been able to do really can shed some light into why tumors metastasize but also shed some light into what we potentially may need to target in specific subsets of breast cancer.

Interviewer – Angela Colmone
Dr. Chan, thank you so much for joining us today, and congratulations on a fascinating paper.

Interviewee – Timothy Chan
Thanks for having me on.

Host – Angela Colmone
That was Timothy Chan of the Memorial Sloan-Kettering Cancer Center in New York. Check out his paper on the *Science Translational Medicine* Web site at stm.sciencemag.org.

I'm Angela Colmone, thanks for listening!

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