Tae Hoon Kim: Knows his boundaries

Kim studies boundaries, promoters, and all manner of gene regulatory elements at the genome-wide scale.

When and where a gene is expressed depends on its associated regulatory elements, chromatin environment, transcription factors, and numerous other influences that scientists do not yet fully understand. Because each gene has a particular expression pattern, it can be difficult to identify general rules for the switching on or off of genes.

Tae Hoon Kim is not perturbed by the difficulties. Although he started out studying regulation of one particular gene—*interferon* β (1), he quickly got a taste for taking his regulation studies genome wide. As a postdoc with Bing Ren, Kim used ChIP on chip (Chromatin immunoprecipitation on microarrays) to map the promoters of nearly 8,000 genes in the human genome (2). He then did a similar large-scale mapping project for potential insulator elements, which form boundaries to the spread of hetero- or euchromatin (3). He has also contributed to the Encyclopedia of DNA elements (ENCODE)—a project to identify all functional elements in the human genome (4).

"I hadn't been a very good student in Korea. I was more interested in playing baseball."

Kim now runs his own laboratory at Yale, where he is particularly concerned with investigating gene regulatory perturbations associated with cancer.

YOUNG STARTER

Where did you grow up?

I was born in Seoul, Korea, and lived there until I was 12. Then I came here to the States. My parents initially settled down in Los Angeles, so I went to grammar school there and started junior high. Then we moved to Fresno, California, where I finished high school.

What was it like moving over from Korea to the US?

I didn't speak any English when I came here. And I hadn't been a very good student in Korea. I was more interested in playing baseball. My mom was always pulling me back home from the baseball field to make me do my homework. She also had to visit the school several times to talk to the teachers because I had problems.

But moving to the States, things changed dramatically. The schools are quite different. And I was also probably becoming a bit more mature.

How do the US and Korean schools compare?

The class sizes are smaller here in the States, so there's more attention given to students. In elementary school in Korea I was in classes with 70 students. So it's more factory style. They do a really good job, setting a high standard for a large number of students. But if a student doesn't fit the mold, they might fall through the cracks.

When did your interest in science begin?

I think I can give a large amount of credit for my scientific career to my high school teacher, Tim Thomas. He wasn't a science teacher, but he was responsible for students participating in science projects. He motivated us to study independently. Because of him, I taught myself a lot of things that were outside of the high school curriculum. I remember during my junior year, around age 16, he gave me a copy of *Recombinant DNA*; a textbook by Jim Watson. I was hooked. I went to the library and found Tom Maniatis's *Molecular Cloning: A Laboratory Manual*. That was really inspirational because it had a whole rationale of how to do bench work.

It prompted me to set up a little molecular biology laboratory in the back room of the high school chemistry laboratory. I had a micro-centrifuge, and I built a couple of gel boxes. And I purchased some equipment thanks to a mini-grant from the PTA.

Early practice for writing grant applications!

Yeah, now it's a lot harder. I wish I didn't have to write grants.

Tae Hoon Kim

FROM GENE TO GENOME

Where did you go to college?

I attended Reed College in Portland, Oregon. It's a small liberal arts college. I studied biology, and at one point I wrote an essay for one of my classes about a paper from the late 1960s by a famous microbiologist named Mark Ptashne. My professor pulled me aside and said, "Did you know Mark Ptashne went to Reed College?"

Then when I started at Harvard as a grad student, Mark Ptashne was actually still there. So I got some interesting advice from him early in my career.

And at Harvard you studied with Tom Maniatis.

Yes. And Maniatis had done his postdoc with Mark Ptashne, so there's a connection.

What did you study?

I worked on a large protein complex that controls gene expression called an enhanceosome. The particular enhanceosome I focused on regulates the *interferon* β gene. I figured out how the whole complex—approximately seven proteins—assembled on DNA.

What made you switch from studying regulation of one gene to studying transcription at the genome-wide scale?

Soon after I started grad school, some papers came out about the technique of chromatin

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Text and Interview by Ruth Williams
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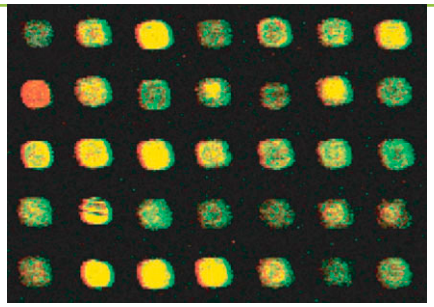


Kim uses ChIP on chip to look for gene regulatory elements in the human genome.

immunoprecipitation. Tom's laboratory was one of the first to apply this technique to human cells. Some people in the laboratory started looking at histone modifications at the interferon locus. But Bing Ren, a graduate student in the laboratory who was four years ahead of me and who became my postdoc mentor later on, started to try ChIP cloning in yeast. He left Maniatis's laboratory and joined Rick Young's laboratory in order to develop the ChIP-chip technique, and then started his own laboratory.

After I graduated in 2002 I had several options of where to go, but I saw a lot of potential with Bing's technique and with being in his laboratory. So we started talking and tried to figure out how to apply his technique to the human genome. Our first human genome-wide paper from Bing's laboratory came out in 2005.

We used antibodies against the preinitiation complex as a way of identifying promoters. It was a good way to test the system, as many promoters were well characterized. But even though it was a straightforward technical paper, it still gave us some unexpected results.

Such as?

There are a number of genes that have two or more alternative promoters. And in general it was thought that the different promoters are used in distinct cell types. But what we found in a large number of cases was that in fact genes would employ both promoters in the same cell type.

Have you got to the bottom of this inconsistency?

We have for one gene—a cell cycle regulator. This gene has two promoters, and they seem to alternate depending on the cell cycle stage. So in a population of cells, activity from both promoters will be seen, but in each individual cell probably only one promoter will be active at a time, depending on the stage of the cell cycle. For other genes, though, we don't know what might be responsible, so we still need to figure out what's going on.

So from genome-wide analyses you need to again bring your focus down to individual genes.

Yes, exactly.

BREAKING BOUNDARIES

What else are you working on?

We're looking at large domains of heterochromatin in cells. It's known that an insulator protein called CTCF marks the boundary where these domains stop. We have defined these boundaries for more than 300 loci in the genome and are now trying to figure out how they function.

These boundaries are interesting because if they are compromised somehow, for example in cancer cells, the heterochromatin could spread to nearby genes, causing silencing.

Do such boundaries change in different cell types as well as in cancer?

They seem to be relatively stable, but there are some changes. For instance, if you look in fibroblasts at the HoxA locus—a cluster of genes that show colinearity of expression and are important in development—the spread of heterochromatin from the 3′ end to the 5′ end of the cluster depends on where in the body the fibroblasts come from. Fibroblasts isolated from the upper body tend to have heterochromatin at the 3′ end of the HoxA locus, and fibroblasts isolated from the foot tend to have the 5′ end heterochromatinized. Interestingly, though, the same boundary is being used in the different fibroblasts.

The boundary behavior at this particular site seems to be distinct from most other insulators in the genome. So we're trying to work out what's going on there, but also we'd like to know if there's a general mechanism to boundary function.

How do you plan to study that?

By transposing the elements into a reporter system, we can analyze the nitty-gritty details, manipulate the sequence, and so on.

Are you working on any other projects?

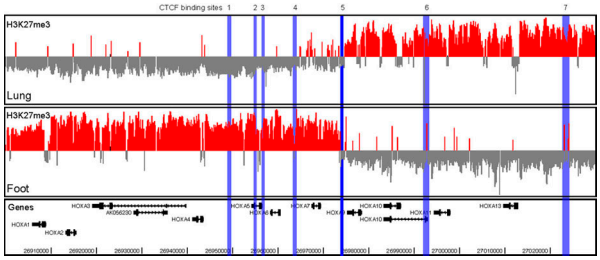
We have a continuing interest in enhancers, particularly ones that might play a critical role in cancers. So we have made some genome-wide maps of enhancers that are relevant for cancer. We found certain genes that are controlled by these classes of enhancers, and we're trying to figure out what the underlying mechanism is.

"I saw a lot of potential with Bing's technique... So we started talking and tried to figure out how to apply his technique to the human genome."

It seems that trying to find unifying mechanisms for gene regulation is pretty tough.

It is. Usually, a grand theory gets proposed, and then people basically figure out all the contrary cases. I think that it's really fun to be a contrarian, but it's much harder to come up with grand theories. And I like a challenge, so I think I'm more of a lumper than a splitter. JCB

1. Kim, T.K., et al. 1998. *Proc. Natl. Acad. Sci. USA*. 95:12191–12196.
2. Kim, T.H., et al. 2005. *Nature*. 436:876–880.
3. Kim, T.H., et al. 2007. *Cell*. 128:1231–1245.
4. ENCODE Project Consortium. 2007. *Nature*. 447:799–816.



Kim has found that, although the boundary elements (blue) are the same in fibroblasts from the upper body (lung) as from the lower body (foot), the heterochromatin marks (red) are differently distributed.

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