Scientists

An Instinct for Science

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Marisa Bartolomei's role in identifying imprinted genes and her subsequent research on epigenetics caught our attention. Curious to know more, *BioTechniques* contacted her to find out about the ambition, character, and motivations that led to her success.

Was there a pivotal event that led to your current research focus?

In 1990, I was a postdoctoral fellow working for Shirley Tilghman at Princeton University and we had two bizarre results in the lab. First, we couldn't make transgenic mice with full-length *H19* (the main gene that I work on) but were successful using a truncated sequence, or minigene. And second, the transgene was expressed when it came from mom, but repressed when it came from dad; every other well-studied imprinted transgene at that time showed the opposite pattern.

We knew then that maternal and paternal genomes were both required for normal development. Bruce Cattanach from the Medical Research Council in the UK had generated mice with uniparental disomies for certain chromosomes that died or showed behavioral phenotypes, indicating that for normal development, all genes on a given chromosome couldn't come from mom and none from dad or vice versa. From human genetics studies, we also knew that some deletions led to disease when inherited from one parent. For instance, Prader-Willi syndrome occurs when a deletion in a certain region of chromosome 15 comes from dad. Although we had no idea what genes were responsible for this, it was clear that there was dosage sensitivity and that genes in particular regions must be imprinted. So Shirley and I decided to see if *H19* was imprinted, but for different reasons: she was interested in the dosage sensitivity while I was interested in the inheritance pattern.

The most exciting moment in my career was watching the film come out of the processor and realizing that the RNA product always came from the maternal allele. We published that *H19* was imprinted in *Nature* in 1991.

What is currently the most important research question in your discipline?

After fertilization, reprogramming occurs to make pluripotent embryos. But imprinted genes don't get reprogrammed at this stage. They get reprogrammed only once when a somatic cell with both maternal and paternal imprints becomes a gamete, which must be designated as male or female. There are about 100 imprinted genes in mammals that must be marked with their parental origin and survive reprogramming after fertilization. The question is how that marking occurs, and how the epigenetic machinery determines that these particular genes, surrounded by the tens of thousands of other genes in the genome, must maintain their parental identity. This is the main focus of our lab.

What other goals are you working toward?

Another interest of the lab is the effect of environmental perturbations on epigenetic regulation. A number of years ago, we were trying to understand if genes were imprinted from the moment of fertilization or if they acquired imprints later in development. By isolating very early embryos from normal mouse matings, we showed that *H19* was imprinted from its first expression in blastocysts. But at the same time, Azim Surani's group at the University of Cambridge found that *H19* was expressed from both alleles, which was really confusing to us initially.

To study imprinting, the maternal and paternal alleles have to be distinguished. We do this by breeding different mouse strains together and looking for single nucleotide polymorphisms (SNPs). Today we can just look on the Internet to choose suitable SNPs since the genomes are sequenced for many mouse strains. But in those days, there weren't many identified SNPs, so we used divergent strains of mice that were difficult to breed. To work around this, Surani's lab used in vitro fertilization to generate F1 hybrid embryos.

Courtesy of Mark Stehle Photography.

Our labs came together to compare cultured embryos with embryos derived from natural matings. We saw that culturing and manipulating the embryos caused a loss of imprinted gene expression that was usually associated with changes in DNA methylation. We are still pursuing this.

Have you ever developed a hypothesis in an unusual way?

Ten years ago, I attended an American Society of Human Genetics meeting in Philadelphia. There was a session on Barker's hypothesis, which came from studies following the Dutch famine caused by World War II. Barker discovered that women who were pregnant during these famine periods often had healthy babies, but when grown, the children had a higher incidence of adult-onset diseases such as diabetes and heart disease. I presented the imprinting differences between cultured and in utero embryos in this session.

In the following session, one of the speakers mentioned as an aside that his Angelman syndrome patient was conceived through assisted reproduction. After the talk, several people spoke up saying that they had Angelman or Beckwith-Wiedemann syndrome patients who were also conceived through assisted reproduction. That discussion was the dawn of a perceived trend of a higher incidence of imprinting diseases with assisted reproduction.

I do science instinctively, doing what feels right rather than following a precedent in the literature, so I decided to pursue the idea that the effects of techniques employed in assisted reproduction might alter epigenetic regulation. Our research in this area has become more translational as we identify the aspects of the technology causing these perturbations with the hope of minimizing them.

Interviewed by Kristie Nybo, Ph.D.

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