Visualizing allele-specific expression in single cells reveals epigenetic mosaicism in an H19 loss-of-imprinting mutant (2016)

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Background

One of the challenges that physicians and scientists face in understanding how imprinting genes work is what is happening at the level of the individual cell. Beckwith-Wiedemann syndrome (BWS) and Russell-Silver syndrome are imprinting disorders due to alterations on chromosome 11. Imprinting controls gene expression by adding methyl groups to DNA, turning genes on or off. Improper methylation can lead to either loss or gain of expression of a specific gene and can result in various epigenetic disorders, such as BWS.

Due to imprinting, some genes are normally only expressed in one of their copies. When a loss of imprinting event occurs – for example, change in methylation at an imprinting control region, this expression can shift to expression from both copies. The ratio of expression between the maternal and paternal alleles of a particular gene in a cell may differ between cells – so even cells from the same part of the body may differ in gene expression. However, the technology to study allelic expression on a single-cell basis did not exist until very recently. Previous methods could only study populations of cells, thereby averaging out individual cell differences.

Using a new procedure called SNP FISH (Single Nucleotide Polymorphism Fluorescent In-Situ Hybridization), it is now possible to test for differences in allelic gene expression at the single-cell level. SNP FISH allows us to find out two things. Firstly, RNA can be traced back to the maternal or paternal allele that made it. Secondly, the quantities of RNA produced by each allele can be estimated, thereby indicating level of gene expression.

Purpose

To determine what happens at the level of the individual cell in a mouse model of imprinting disorders. Specifically, whether imprinting is altered in every cell a little bit or altered completely in some cells and normal in other cells resulting in mosaicism.

Methods

Using skin cells from a mouse model of imprinting alterations on mouse chromosome 7 (similar to human chromosome 11), the SNP FISH technique was used to look at the expression of *H19* and *IGF2* (genes that are altered in BWS) in individual cells for hundreds of cells.

Key Points

- In mice cells with alterations in imprinting, cells from the same tissue form two groups, one where genes are expressed normally and one where expression is altered as seen in BWS.
- As they grow and divide, cells do not change this specific gene expression pattern of the imprinted genes.
- These differences in expression are directly due to whether the cells have normal or altered methylation.

Reference

Ginart P et al. Visualizing allele-specific expression in single cells reveals epigenetic mosaicism in an H19 loss-of-imprinting mutant. *Genes Dev.* 2016;30(5): 567-78. PubMed PMID: 26944681