This Month in Genetics

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Two Signaling Pathways Involved in Myelodysplastic Syndrome

One of the most common subtypes of myelodysplastic syndrome (MDS) is associated with a recurrent deletion on chromosome 5q. People with the 5q− syndrome have a chronic, severe anemia that is often refractory to standard treatment, and they have dysplastic megakaryocytes in their bone marrow. The critical region for 5q− syndrome is a 1.5 Mb region that contains at least 24 genes, making it difficult to tease apart the mechanism that leads to MDS. Two recent papers in *Nature Medicine* take very different approaches to this problem, and each identifies what appears to be a key pathway involved in 5q− syndrome. Starczynowski et al. looked for microRNAs in the 5q− critical region and found two, miR-145 and miR-146a, that are expressed at lower-than-normal levels in bone marrow samples from people with MDS. Reduced expression of these miRNAs, in turn, leads to increased activation of innate immune signaling in hemoatopoietic stem and progenitor cells, including elevated IL-6 expression. This is not the same pathway implicated in 5q− syndrome by Barlow et al., who used chromosome engineering methods to delete mouse chromosomal regions that are syntenic to the human 5q− critical region. A deletion on mouse chromsome 18, which includes *Rps14*, leads to macrocytic anemia and abnormal megakaryocyte development, features that resemble MDS. Many of these hematopoietic deficits are rescued when these mice are crossed to a *Trp53*$^{-/-}$ strain, implicating p53 signaling in the development of 5q− syndrome. Together, these papers suggest that a single gene in the 5q− critical region is not the key to the development of MDS. Rather, they implicate two separate signaling pathways as being important for development of this syndrome.

Starczynowski et al. (2010). Identification of miR-145 and miR-146a as mediators of the 5q- syndrome phenotype. Nat. Med. 16, *49–58.*

Barlow et al. (2010). A p53-dependent mechanism underlies macrocytic anemia in a mouse model of human 5q- syndrome. Nat. Med. 16, *59–66.*

Boy, Are You Different!

If you look at our autosomes, it is remarkable how similar we are in DNA sequence to chimpanzees. The unique nature of the Y chromosome suggests it has evolved through different mechanisms than the rest of the genome, and some have predicted that the Y chromosome might actually be more similar between humans and chimps than is the rest of the genome. In fact, the opposite is true. The first high-resolution sequence of the chimpanzee Y chromosome has been completed by Hughes et al., who find dramatic differences in the chimpanzee Y chromosome compared to the human Y. Almost one-third of the male-specific sequence on the chimpanzee Y chromosome is not found on the human Y, and vice versa, whereas less than 2% of sequence lacks a human counterpart in other parts of the genome. Many of these unique sequences on the two Y chromosomes are found in the palindromic regions, which have the potential for rapid structural change. The palindromic regions on the chimpanzee Y chromosome are even more complicated than those on the human Y; there are many more palindromes on the chimp Y, and most of them exist in multiple copies. These features provide more potential substrates for inter- and intra-chromosome nonhomologous allelic recombination. Although structurally more complicated, however, the chimp Y encodes far fewer genes and gene families than the human Y. If this is what we see in our closest relative, imagine the differences that we might see as more Y chromosomes are sequenced.

Hughes et al. (2010). Chimpanzee and human Y chromosomes are remarkably divergent in structure and gene content. Nature. Published online January 13, 2010. 10.1038/nature08700.

Identifying the Achilles Heel of the Tasmanian Devil

The Tasmanian devil population is endangered because of a transmissible cancer, devil facial tumor disease (DFTD), that has decimated the population. You might immediately think DFTD must be caused by a virus, but this rapidly fatal cancer is actually passed between animals as a clonal allograft when they bite each other. The lack of diversity in the species contributes to the problem by limiting the immune recognition of this allograft as a foreign invader. Beyond this, very little is known about DFTD, and there is a lack of diagnostic tests and therapies for the disease. Murchison et al. figured one of the first things to know would be the identity of the tissue in which the original cancer arose, and they determined this through expression profiling of tumors. Gene expression in DFTD tumors most closely resembles the expression profiles of peripheral nerves, implicating this tissue as the

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origin of the tumor. Although it's the tip of the iceberg, this knowledge lets us begin to think about how this cancer arose and why it can spread so effectively. The findings also have a direct and immediate diagnostic application. Murchison et al. tested expression of several peripheral nerve proteins in DFTD tumors in the hopes of identifying a histological marker for DFTD. They found that the normally Schwann-cell-specific protein periaxin was expressed in all of the DFTD tumors and mestastases tested, making it the first diagnostic marker for the disease. This test could help with the management of the infection in Tasmania because it allows for the identification of infected devils so that they can be isolated to potentially limit the spread of the infection.

Murchison et al. (2010). The Tasmanian devil transcriptome reveals schwann cell origins of a clonally transmissible cancer. Science 327, *84–87.*

Axon Misguidance Due to Defective Microtubules

Functional microtubules are a requirement for proper development of the nervous system. Mutations in particular tubulin isotypes have already been identified as causes of lissencephaly and polymicrogyria, defects that apparently result from aberrant neuronal migration. Tischfield et al. now report that one type of tubulin, the neuron-specific β-tubulin isotype III that is encoded by *TUBB3*, is needed for proper axon guidance rather than neuronal migration. *TUBB3* mutations cause a range of nervous system disorders that all include ocular motility problems due to hypoplasia of the oculomotor nerve. In addition to isolated defects of the eye, other features of these syndromes can include dysgenesis of the corpus collosum and progressive sensorimotor polyneuropathy. A total of 29 unrelated families had missense *TUBB3* mutations, many of them recurrent. To some extent, the precise mutation present in a family can suggest the clinical outcome, and the authors used a variety of experimental systems to explore the molecular defects associated with each mutation. Differences in the effects of each mutation on microtubule dynamics, heterodimer formation, and the interactions of the microtubules with kinesin proteins might at least partially explain the genotype-phenotype correlations.

Tischfield et al. (2010). Human TUBB3 mutations perturb microtubule dynamics, kinesin interactions, and axon guidance. Cell 74, *74–87.*

Conserved Role in Meiotic Recombination for the Rapidly Evolving Gene *PRDM9*

Meiotic recombination in mammals tends to occur preferentially at certain sites, termed hotspots. At least for some hotspots, the DNA sequence in the region is involved in selection of the site of recombination, including a 13 bp motif that is overrepresented at human hotspots. How did these hotspots evolve, given that the process of recombination means that the noninitiating allele is used as a template for gene conversion to correct the initiating, recombination-prone allele, giving rise to the "recombination hotspot paradox"? Three recent papers suggest that the same protein, PRDM9, controls the location of recombination hotspots in humans and in mice, and they suggest that this gene displays a striking evolutionary pattern that may counteract the recombination paradox. PRDM9 is a zinc-finger protein that recognizes the human hotspot motif. Variation in this gene explains a significant fraction of interindividual variation in hotspot usage in humans. Similarly, variation in murine *Prdm9* controls hotspot usage, suggesting conservation of this system in mammals. Yet the work by Myers et al. demonstrates that chimpanzee PRDM9 does not recognize the same hotspot motif used in humans, which at least partially explains the fact that humans and chimpanzees do not share recombination hotspot motifs. Sequence comparisons between mammalian species indicate that *PRDM9* is a rapidly evolving gene, and this could tie into the lack of conservation in recombination hotspots between species. Changing even a single amino acid in one of PRDM9's zinc fingers appears to be able to confer new DNA sequence specificity for protein binding, which could explain the creation of new hotspots. Thus, although the recombination paradox would appear to be removing hotspots from genomes, positive selection on the binding specificity for PRDM might have counteracted this loss by driving the protein to recognize new DNA motifs as hotspots.

Myers et al. (2009). Drive against motifs in primates implicates the PRDM9 gene in meiotic recombination. Science. Published online December 31, 2009. 10.1126/science.1182363.

Parvanov et al. (2009). Prdm9 controls activation of mammalian recombination hotspots. Science. Published online December 31, 2009. 10.1126/science.1181495.

Baudat et al. (2009). PRDM9 is a major determinant of meiotic recombination hotspots in humans and mice. Published online December 31, 2009. 10.1126/science.1183439.

This month in Our Sister Journals

Detection of Mosaicism by Array CGH

With traditional cytogenetic analysis, the chromosomes from individual cells are analyzed, so it is straightforward to find cell-to-cell variation in chromosome structure, which can reflect underlying mosaicism. The sensitivity for detection of mosaicism with this approach is determined by the number of cells analyzed. With array-based comparative genomic hybridization (aCGH), in contrast,

DNA from multiple cells is simultaneously bound to the array for analysis. Use of aCGH increases the resolution for detection of cytogenetic abnormalities, but the sensitivity of oligonucleotide-based aCGH for detection of mosaicism is not clear. Scott et al. assessed this sensitivity by spiking arrays with known ratios of normal to abnormal samples. They report that, with the right analysis, they can detect mosaicism for aneuploidy when it is present at a level as low as 10% and for segmental aneuploidies when these composed 20%–30% of the sample. A word of caution, though: these levels of detection were only achieved through use of dye-swap replicates and in the absence of data filtering, a procedure that would increase false-positive results in routine use. Traditional cytogenetic analysis of cultured cells was also compared to analysis of uncultured cells by aCGH. This yielded an unexpected finding —discordant results between the aCGH and the karyotype from cultured cells, particularly for double aneuploid samples. The authors believe that aCGH was able to detect previously unidentified placental mosaicism, but the discrepancy between the results suggests that caution should be used in the interpretation aCGH performed on uncultured cells.

Scott et al. (2010). Detection of low-level mosaicism and placental mosaicism by oligonucleotide array comparative genomic hybridization. Gen. Med. 10.1097/GIM.0b013e3181cc75d0.