This Month in Genetics

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Coordination of Lysosome Biogenesis

Are lysosomes garbage dumps that sit and wait for cellular trash, or are they a more dynamic organelle whose activity is coordinated with cellular needs? Sardiello et al. reasoned that because the degradation needs of cells vary, there should be a mechanism of coordinating lysosome production and activity, and their recent work describes the discovery of such a regulatory network. They found that lysosomal genes are expressed in a coordinated fashion that is at least partly due to a 10 bp palindromic sequence motif found near the transcription start site of these genes. This motif, which they dub the CLEAR motif (Coordinated Lysosomal Expression And Regulation), mediates transcriptional activation of the genes, apparently through interactions with the transcription factor TFEB. MicroRNAs, such as miR-128, downregulate TFEB, which in turn reduces expression of several lysosomal genes. This regulatory mechanism is presumably used when less lysosomal activity is needed. Under conditions of aberrant lysosomal storage, on the other hand, TFEB translocates to the nucleus and induces an expansion of the number of lysosomes in cells, which increases their degradative capacity. In fact, cells overexpressing TFEB are better able to degrade glycosaminoglycans and to clear mutant huntingtin. This regulatory network is a new therapeutic target for diseases whose hallmark is an accumulation of toxic macromolecules.

Sardiello et al. (2009). A gene network regulating lysosomal biogenesis and function. Science Express, in press. Published online June 25, 2009. 10.1126.science.1174447.

The Existence of X Chromosome Inactivation without *Xist*

In order to compensate for the fact that they have twice as many copies of the X chromosome as males, female mammals must silence most of the genes on one copy of the X chromosome in each cell. An accumulation of evidence suggests that the first step in this process is the expression of a noncoding gene, *Xist*, from the X chromosome that will be inactivated. Xist RNA spreads in *cis* from the site of its encoding gene to coat the inactive chromosome. We know that, in mice, the paternal X chromosome is preferentially inactivated in early embryos and that this so-called imprinted X chromosome inactivation (XCI) is maintained in extraembryonic tissues. Kalantry et al. made use of this preference to show that *Xist* is not absolutely required for initiation of imprinted XCI; early female embryos that inherit a null allele of *Xist* on the paternal allele are still able to shut off the paternal expression of several X-linked genes. Other X-linked genes are more sensitive to the effects of *Xist* and are biallelically expressed in the embryos. Although initiation of imprinted XCI does not absolutely require *Xist* expression, extraembryonic tissues cannot maintain imprinted XCI in the absence of *Xist*, indicating that *Xist* is required for stabilization of imprinted XCI during postimplantation development. The discovery of *Xist*-independent XCI points to the existence of another mechanism for XCI initiation.

Kalantry et al. (2009). Evidence of Xist RNA-independent initiation of mouse imprinted X-chromosome inactivation. Nature, in press. Published online July 1, 2009. 10.1038/nature08161.

A New Role for Telomerase

Without telomerase, chromosome ends progressively shorten as cells divide, and the cells eventually become senescent. Although an effective protection against uncontrolled cell division, this is clearly a problem for stem cells, which must maintain the ability to divide. Indeed, telomerase expression and its activity in maintaining telomere length are crucial for stem cell maintenance. Park et al. have revealed a surprising new pathway by which telomerase is involved in stem cell renewal. The telomerase protein component, TERT, is a component of β-catenin transcriptional complexes that participate in Wnt signaling. In mouse embryonic stem cells, TERT is required for Wnt3A stimulation of Wnt target genes to their full extent. In *Xenopus* embryos, depletion of TERT causes a defect in anterior-posterior axis formation that is similar to what is observed in embryos deficient for components of the Wnt pathway. The role of telomerase in Wnt signaling does not require its RNA component, nor does it require the documented enzymatic activity of TERT. Thus, this work defines a completely new role for telomerase in stem cell renewal, a role that could serve to coordinate the regulation of progenitor cell proliferation and telomere maintenance.

Park et al. (2009). Telomerase modulates Wnt signaling by association with target gene chromatin. Nature 460, 66–72. 10.1038/nature08137.

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DOI 10.1016/j.ajhg.2009.07.005.

Man versus Machine

Who among us hasn't at some point felt that if only we had more time to read the literature, our research would come together faster? Raychaudhuri et al. have now come up with a way for human geneticists to mine the literature in an automated fashion to identify disease genes. Their statistical method, called GRAIL, uses text mining of PubMed abstracts to assess genomic regions that have been pulled out of genome-wide association studies. By comparing abstracts describing research on the genes in these regions, GRAIL can identify the subset of regions with related genes, which presumably could function in a common pathway. In the process, GRAIL identifies the likely candidate gene in each region. In testing the method on a data set from a Crohn disease association meta-analysis, GRAIL was more likely to identify as important those regions that have subsequently been replicated for their association with Crohn disease. The authors also use GRAIL to examine the rare deletions that have been identified in samples of schizophrenia patients and matched controls. For the deletions found in the cases, GRAIL identified a subset that encompassed highly related genes that are preferentially expressed in the central nervous system; in contrast, no significant relationships were identified between genes in the regions deleted in controls. As the authors admit, GRAIL doesn't do anything that a researcher with a lot of time on her hands couldn't theoretically do, but GRAIL is an automated and, perhaps more importantly, unbiased way to review the literature for identification of biological pathways that are key to disease pathogenesis.

Raychaudhuri et al. (2009). Identifying relationships among genomic disease regions: Predicting genes at pathogenic SNP associations and rare deletions. PLOS Genetics 5, e10000534. 10/1371/journal/pgen.1000534.

Variation Generation

The more closely we look at the human genome, the more variation we find, but the origin of this variation remains, to some extent, a mystery. Jim Lupski's group has been analyzing nonrecurrent rearrangements by using oligonucleotide array comparative genomic hybridization (array CGH). They proposed a DNA replication-based mechanism for the formation of these rearrangements, in which stalling of replication at the active replication fork can lead to switching of the DNA template via microhomology between the original and new template strands. The microhomology can be very short, as little as two base pairs in length. This model is called FoSTeS, for fork stalling and template switching. In their current work, Zhang et al. use oligo array CGH and sequence analysis to study nonrecurrent rearrangements on chromosome 17p11.2 and 17p12, many of which turn out to be more complex than was apparent from methods with lower resolution. The authors believe that the FoSTeS model could explain the origin of many of these rearrangements, which can range in size from a few hundred base pairs to several megabases. Although some of the rearrangements appear to be the result of a single template-switching event, others seem to derive from two, or even three, template switches. FoSTeS-mediated rearrangements do not seem to be limited to chromosome 17. In their analysis of complex rearrangements in the Human Gene Mutation Database, Zhang et al. found microhomologies at the breakpoints in at least 17 genes. FoSTeS, therefore, could turn out to be a major source of variation that acts at the single gene and at the genome scale.

Zhang et al. (2009). The DNA replication FoSTeS/MMBIR mechanism can generate genomic, genic and exonic complex rearrangements in humans. Nature Genetics 41, 849–854. 10.1038/ng.399.

This Month in Our Sister Journals

Finding Common Ground to Assess Direct-to-Consumer Genetic Testing

The August issue of *Genetics in Medicine* is devoted to personal genomics. An accompanying commentary by Editor-in-Chief Jim Evans and Robert Green discusses the controversy surrounding direct-to-consumer genetic testing. On one side there appears to be a group that argues that genetics professionals can be paternalistic about how much patients should know. On the other side is a group that feels that giving patients too much information could be harmful. The authors urge the genetics community to find some common ground to discuss these issues, and they stress a set of points that they feel should be considered as the debate moves forward.

Evans, J.P. and Green, R.C. Direct to consumer genetic testing: Avoiding a culture war. Genetics in Medicine, in press. Published online July 14, 2009. 10.1097/GIM.0b013e3181afbaed.

Coworkers

Sometimes the work of those around you can be important for your own occupation. This is the thinking that led Cziko et al. to look for proteins that interact with the

fragile X mental retardation protein (FMRP). FMRP is involved in local control of protein synthesis in neurons. Loss of FMRP expression, and presumably the resulting misregulation of protein translation, leads to mental retardation. FMRP is an RNA-binding protein that is a component of ribonucleoprotein granules in neurons, but we don't fully understand how it is involved in translational regulation. Cziko et al. reasoned that finding proteins that work in concert with FMRP might help us better understand FMRP function, and they took a genetic approach to finding these partners. They made use of the fact that overexpression of the *Drosophila FMR1* gene, *dFMR1*, in the fly eye leads to an easily scorable rough eye phenotype. They tested loss-of-function alleles in a series of candidate genes and found five that suppressed the rough eye phenotype. These range from a splice factor, to polyA-binding protein, to a kinase. Supporting the role of the encoded proteins in translational control are data showing that the proteins are found in neuronal granules and that when they are overexpressed, they inhibit dendritic growth. Although FMRP has been implicated in the miRNA pathway, loss of function of dFMR1 or of any of the interacting proteins identified in this study did not noticeably alter the function of the *bantam* miRNA in a reporter assay. Whether this holds true for additional miRNAs remains to be seen.

Cziko, A.M., McCann, C.T., Howlett, I.C., Barbee, S.A., Duncan, R.P., Luedemann, R., Zarnescu, D., Zinsmaier, K.E., Parker, R.R., and Ramaswami, M. Genetic modifiers of dFMR1 encode RNA-granule components in Drosophila. Genetics, in press. Published online June 1, 2009. 10.1534/genetics.109.103234.