MED12 mutations and uterine fibroids

Uterine leiomyomas, or fibroids, are benign tumors arising from the smooth-muscle layer of the uterus that can produce a range of clinical symptoms. A new study by Lauri Aaltonen and colleagues (*Science*, published online 25 August 2011; doi:10.1126/science.1208930) now shows that a majority of uterine leiomyomas harbor mutations in *MED12*, an X-chromosome gene that encodes a subunit of the Mediator complex implicated in transcriptional regulation. The authors performed exome sequencing of 18 uterine leiomyomas and matched normal tissue and found somatic mutations of *MED12* in 10 tumors. Notably, all of the mutations clustered in exon 2, with eight mutations affecting codon 44. Sequencing of this region in 207 additional uterine leiomyomas identified *MED12* mutations in 70% of tumors, with codon 44 altered in 49% of tumors. Previous studies have reported germline mutations at codons 961 and 1007 of *MED12* as the most frequent causes of Opitz-Kaveggia and Lujan-Fryns syndromes, two rare congenital disorders that are not associated with tumor susceptibility. The clustering of *MED12* mutations to exon 2 in uterine leiomyomas suggests that a distinct molecular mechanism underlies the selection for *MED12* mutations in these tumors. ***KV***

Sexually dimorphic digits

The ratio between the second digit (2D) and fourth digit (4D) length differs between human males and females. 2D is generally shorter than 4D in males (2D:4D < 1), whereas 2D is typically the same or longer than 4D in females (2D:4D ≥ 1). Zheng and Cohn report (*Proc. Natl. Acad. Sci. USA*, published online 6 September 2011; doi:10.1073/pnas.1108312108) that similar 2D:4D sexual dimorphism occurs in mice and that it is regulated by the balance of androgen to estrogen signaling *in utero*. The difference in androgen receptor (AR) activity between 2D and 4D was greater in males, whereas the difference in estrogen receptor (ER-α) activity was greater in females, suggesting that the relative difference in androgen versus estrogen activity controls this trait. Males lacking AR showed increased 2D:4D ratios, whereas males lacking ER-α had decreased 2D:4D ratios. AR thus seems to be required for the masculine (low) 2D:4D ratio, whereas ER-α is needed for the feminine (high) 2D:4D ratio. Inhibiting AR pharmacologically caused a 40% reduction in chondrocyte proliferation in 4D but only a 20% reduction in 2D, accounting for decreased growth of 4D and the subsequent increased 2D:4D ratio. In contrast, inactivating ER-α increases growth of 4D, leading to a lower 2D:4D ratio. The authors conclude that the 2D:4D ratio is controlled by uterine hormones, implying that the 2D:4D ratio may be a valid index of uterine environment. *PF*

Selfish switch in honeybee workers

Sterile worker castes in eusocial insects have been attributed to kin selection theory, in which the reproductive success of a relative is favored, even at the expense of one's own survival and reproduction. In honeybee workers, reproduction is prevented by queen and brood pheromones and by worker policing. However, in the Cape honeybee subspecies, laying workers can act as social parasites by invading foreign colonies, reproducing and becoming pseudoqueens. These traits have previously been mapped to chromosome 13, and now Robin Moritz and colleagues show that alternative splicing of the honeybee *gemini* gene regulates sterility in workers (*Proc. Natl. Acad. Sci. USA*, published online 6 September 2011; doi:10.1073/pnas.1109343108). Laying and non-laying Cape workers showed different splice patterns at exon 5 and exon 7 of *gemini*, with undeveloped worker bees producing the full transcript containing exon 5, and laying workers producing a transcript lacking exon 5. The authors knocked down exon 5 in non-Cape worker bees and observed higher reproductive capacity, showing that removing exon 5 function affects worker sterility. Sequencing of the flanking introns in the parasitic Cape honeybees showed a consistent 9–base-pair deletion of an intronic splice enhancer motif. Absence of this motif in Cape honeybees suggests that it may act as a genetic switch sufficient to convert an altruistic worker into a parasite. *PF*

Maternal imprinting defect

Familial biparental hydatidiform mole (FBHM) is a recessive disorder that results in repeated pregnancy loss due to a failure to establish maternal imprints at multiple loci throughout the genome. Previous work showed that some cases of FBHM result from biallelic mutations in *NLRP7* (*Nat. Genet.* **38**, 300–302, 2006). Eamonn Sheridan and colleagues (*Am. J. Hum. Genet.* **89**, 451–458, 2011) now identify mutations in *C6orf211* as a likely cause of FBHM in families not harboring *NLRP7* mutations. Starting with a large consanguineous FBHM family for which linkage to *NLRP7* had been excluded, the authors performed homozygosity mapping followed by targeted capture of all coding sequences from six regions of concordant homozygosity. Bioinformatic filtering for potentially damaging mutations highlighted a variant disrupting the initiation codon of *C6orf221*. Analysis of 14 further cases of recurrent hydatidiform mole identified two additional cases with biallelic inactivating mutations in *C6orf221*. Expression studies in human ovarian follicles, oocytes and preimplantation embryos showed peak *C6orf221* transcript levels in germinal vesicle oocytes, similar to the expression profile previously reported for *NLRP7*, suggesting that the products of these two genes might act in a common pathway required for maternal imprinting. *KV*

A surprising role for FOXO

Activation of the serine-threonine kinase AKT is associated with tumor promotion, whereas its downstream FOXO transcription factor targets are associated with tumor-suppressor functions. Now, David Scadden and colleagues show that AKT and FOXOs have opposite roles from the expected in acute myeloid leukemia (AML) (*Cell* 146, 697–708, 2011). The authors used a mouse model in which AML is induced with a MLL-AF9 fusion protein and showed that leukemic progenitor cells have diminished Akt activity and enhanced FoxO activity compared to normal myeloid progenitor cells. Constitutive activation of Akt or deletion of *Foxo1*, *Foxo3* and *Foxo4* in cultured cells increased expression of markers of myeloid differentiation. *In vivo* Cre-mediated knockout of *Foxo1*, *Foxo3* and *Foxo4* delayed the onset of leukemia and impaired leukemia-initiating cell function. The authors also showed that human AML cell lines with the MLL-AF9 translocation have active FOXO3, and knockdown of FOXO3 increased expression of markers of myeloid maturation and apoptosis and activated the JNK–c-JUN signaling pathway that is involved in myeloid differentiation. Pharmacological inhibition of JNK acted synergistically with knockdown of FOXO3 to increase expression of markers of myeloid maturation and apoptosis. This work suggests that the AKT-FOXO and JNK–c-JUN signaling pathways may be useful therapeutic targets to treat AML. ***EN***

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