Melorheostosis

Current Understanding and Recent Developments

Robert E. Fleming, M.D.
Associate Professor of Pediatrics and Biochemistry & Molecular Biology
Saint Louis University School of Medicine
Clinical Diagnoses

• Osteopoikilosis
  – Autosomal Dominant Inheritance
  – Multiple hyperostotic areas

• Buschke-Ollendorff Syndrome
  – Autosomal Dominant Inheritance
  – Osteopoikilosis with Connective tissue nevi

• Melorheostosis
  – ? Somatic mutation (Segmental type II)
  – Flowing hyperostosis with adjacent soft tissue abnormalities
Radiographic Appearance

Ostopoikilosis

Melorheostosis

www.rad.washington.edu/mskbook/dysplasia.html
Melorheostosis “Candle Wax” Appearance

www.stevensorenson.com/residents6/melorh9.gif
Bone Scan Findings

http://ard.bmjjournals.com/content/vol57/issue8/images/large/98133.f3.jpeg
Associated Problems

- Joint contractures
- Sclerodermatous skin lesions
- Muscle atrophy
- Hemangiomas
- Lymphoedema

www.melorheostosis.org/PIF_Monica.htm
“Segmental” Distribution

- Melo. lesions may correspond to a “sclerotome”
- Sclerotomes reflect the segmental pattern of early development

http://focus.hms.harvard.edu/2003/May2_2003/research_briefs.html
The Sclerotome Forms Cartilage and Bone

Migrating sclerotome cells
Dermatome
Condensation of chondrocytes from sclerotome cells
Myotome
Dorsal aorta
Nephrotome of developing kidney
Intraembryonic coelom
Gut
Somatic mesoderm layer
Splanchnic mesoderm layer
Somatic mesoderm layer

http://classes.aces.uiuc.edu/AnSci312/Bone/Gil%209%205%20Somites%20migration%20human.jpg
Cartilage-Forming Cells Migrate from the Sclerotome to the Limb Buds
Segmental Distribution Suggests a Somatic Mutation

Anomalies found only in certain segments of the myotome, dermatome, or sclerotome may be due to a “somatic mutation,” i.e. a mutation that occurred after embryonic development has begun.

http://members.shaw.ca/copingwithillness/april02Xinact2/sld014.htm
Example of Skin Mosaicism

www.med-ars.it/ galleries/mosaicism.htm

Somatic (Postzygotic) Mutations Lead to “Mosaicism”
MAN1/LEMD3 Mutations and Osteopoikilosis

• Mutations resulting in “loss of function”
• Identified in the LEMD3 gene
  – Also known as the MAN1 gene
  – Also known as XMan1 or SANE in the Xenopus frog
• In patients with:
  – Osteopoikilosis
  – Buschke-Ollendorff Syndrome
  – Osteopoikilosis + Melorheostosis

Hellemans et al Nature Genetics 36: 1213-1218, 2004
MAN1/LEMD3, Osteopoikilosis, and Melorheostosis: A Theory

- Germline-transmitted mutations in MAN1/LEMD3 cause osteopoikilosis
- A second “somatic” mutation in MAN1/LEMD3 causes melorheostosis in bones and tissues derived from the involved segment (“second hit”)
- This second mutation is only expected in the involved tissue
Testing the “2nd Hit” Theory

- Tested theory: No “second hit” found in involved skin tissue
- Osteoblasts not tested
- Entire gene not sequenced
- Second hit gene not MAN1/LEMD3?
MAN1/LEMD3 is Expressed in Multiple Tissues

MAN1/LEMD3 is an Inner Nuclear Membrane Protein

Regions Identified in the MAN1/LEMD3 Protein

- 754 amino acids long
- Has a LEM domain
  - Region identified in three different proteins: LAP2, emerin, MAN1
  - LEM is 40 amino acids long
  - Function of LEM domain is unknown
- Has two membrane-spanning domains
  - Predicted to fold across a membrane

MAN1/LEMD3 Mutations in Different Osteopoikilosis Patients

Hellemans et al Nature Genetics 36: 1213-1218, 2004
What is the MAN1/LEMD3 gene structure?

- 10 exons (rectangles) make up the mRNA
- 9 of these contain sequences encoding amino acids (black rectangles)
What Does MAN1/LEMD3 Do?

• Blocks the signal from Bone Morphogenic Proteins (BMPs) and from TGF-beta
• By Binding to SMAD proteins
• Preventing SMAD proteins from activating certain genes involved in bone formation
• Thus, loss of MAN1/LEMD3 leads to excess bone formation
BMPs

Cell Membrane

Modified from:
BMPs

Cell Membrane

Modified from:
BMPs

Cell Membrane

Nuclear Membrane

BMPs

Cell Membrane

Modified from:
BMPs

Cell Membrane

TGFβ

Cell Membrane

BMPs

TGFβ

Cell Membrane

Nuclear Membrane

Modified from:
BMPs Play a Central Role in Limb Development

- Skeletal structures are first to differentiate (recognizably) in the limb.
- Differentiation into pre-cartilaginous condensates happens centrally, partly because ectoderm inhibits cartilage differentiation. These aggregates begin expressing BMP2 and BMP4, but that expression gradually is restricted to periosteum or perichondrium surrounding the bones. Similarly BMP3 starts in differentiated chondrocytes, but is also restricted to perichondrium as the bones develop.
- BMP-6 (possibly induced by Ihh) is expressed in hypertrophic maturing cartilage.
Endochondral Bone Formation

Bone Growth

Blood vessels
Medullary cavity
Articular cartilage
Spongy bone
Secondary ossification center
Epiphyseal plate
Periosteum
Compact bone
Types of Bone Cells

- osteogenic cell (osteoblast precursor)
- osteoblast
- osteoid (uncalcified bone matrix)
- calcified bone matrix
- cell process in canaliculus
- osteocyte

- bone cells
- osteoblasts (builders)
- osteoclasts (digesters)
- osteocytes (retired builders)
BMPs, TGFβ, SMADs Participate in Multiple Steps in Bone Formation
Unsolved Mysteries

• Is LEMD3 the melorheostosis gene?
• Is melorheostosis due to a somatic mutation?
• Does everyone with a LEMD3 mutation get bone changes?
• What genes are down-regulated by LEMD3?
• What are the compensatory mechanisms in the cell for loss of LEMD3?