Congenital Deformities of Upper Ex. – Molecular Control

Mark Chong
SpR Northern Deanery Hand Term
Congenital Deformity

• Fact 1: Most reviews on congenital deformities are impenetrable.

• Quote from Bamshad et al...

• ‘Comparison of homologous genes TX-12k is advantages because modifiers of developmental programs conserved among closely related species can be identified by regulatory findings of LDH-B1Z locus, whereas the identification of modifiers between taxa is more likely to represent alteration of shared developmental program rather than evolutionary convergence....’
Deformities of Upper Limbs

- 2\textsuperscript{nd} commonest congenital defect after cardiac abnormalities
- 1 in 600 live births
- Classified according to morphological appearance. (Swanson – I Hand Surg 1976)
Swanson Classification for Congenital Hand Deformities

• Formation
• Differentiation
• Overgrowth
• Hypoplasia
• Constriction Band
• Generalised Skeletal Abnormalities
Theory of Evolution

• Roots can be traced back to Darwin’s scientific theory of evolution – process of natural selection
Modern Times Theory – Molecular Level

• 3 main proteins and 2 genes:
• Transcription Factors, Receptors and Ligands
• HOX and T-Box
• Understanding these interactions enable scientist to discover early diagnosis and/or therapeutic control
Normal Development

• Limb bud starts on day 28 – ends at 8\textsuperscript{th} week
• Starts from somites 8 – 10\textsuperscript{th} level.
• Coordinated by proteins and genes.
Mesodermal layers

2 mesodermal layers

- *Somites* – transformed to muscles
- *Lateral plate* – Bones and joints
3 important proteins

• *Transcription Factors, Ligands and Receptors*
• *Ligands* – Proteins that signal neighboring cells to differentiate or populate. (BMP, FGF, Shh)
• *Receptors* – Proteins on cell membrane that binds to ligands. Ligands binding to receptors cause signal transduction leading to change in cellular behaviour.
• *T – factors* – Transmit signal from activated receptor to the cell nucleus. Binds to DNA and express new gene.
Ligands, Receptors and T-Factors
Limb Bud Development

- Limb Formation is a continuation process
- 3 spatial axes – Proximodistal (PD), Anteroposterior (AP), Dorsoventral (DV)
- All axes are governed by proteins with feedback loops to coordinate normal development of limb
- Studies derived mainly from mouse and chicken limbs
PD axis

- Controlled at the *Apical Ectodermal Ridge* (AER). This is a ridge of ectoderm forms between the meeting point of ventral and dorsal layers of ectoderm.
- When AER is surgically removed, PD growth ceases.
- If AER is implanted at remote site, extra limb bud forms
- AER acts by secreting *FGF* proteins
AP axis / Radial Ulna Axis

• Determined early within lateral plate before limb bud formation
• Group of cells from ulna tissue secretes protein that act on AP structures
• Located in zone of polarization activity (ZPA). (posterior part of the limb bud)
• Transplantation of ZPA causes mirror hand.
• Primary growth factor is called Sonic Hedgehog (Shh).
• Shh induces FGF-4 in the AER via positive feedback loop.
• PD and AP axes are not mutually exclusive.
Schematic diagram of a limb bud
Real life Mouse Limb

- Note the position of Shh posteriorly and the AER at the rim of limb bud
DV axis

- Less well understood
- Dorsal ectoderm secretes wingless-type mouse mammary tumour virus integration site family member 7a (Wnt-7a)
- Mice lacking Wnt has biventral limbs
- Wnt-7a induces t-factor called Lmx1 that governs dorsal growth. Lack of Lmx1 – nail patella syndrome
DV axis

• Reciprocally, the ventral ectoderm secretes *engrailed-1 (En1)*
• Mice lacking these has bi-dorsal limb
• Important to realise that axes are not independent of each other.
• *Shh* is thought to be the link between DV and the other axes. Hence single gene defect on *Shh* can lead to complex abnormalities
• What Happens when the complex system goes wrong?
Nail Patella Syndrome due to lack of Lmx-1
Family of T-factors

• Primary axes formation is only one facet of limb development
• Mutation in HOX genes also causes limb deformities. – synpolydactyly.
Syndactyly

- Mutation of *Msx-2* transcription factor
Apert’s Syndrome

• Caused by mutation in FGF receptors
Polydactyly

• Influenced by **BMP (ligands)** and **Gli-3 (T factors)** expressions. BMP-7 & Gli-3 has suppressive role in digit formation. Hence lack of BMP-7 gives rise to extra digits.
Brachydactyly

- Mutation in GDF-5 (member of BMP family)
Holt-Oram Syndrome

Conclusion

• Need to know the basics of limb bud development cascade

• Recognise the 3 axes and that they are not mutually exclusive.

• Potential therapeutic uses. Eg. BMP used in treating non-union. GDF-5 used in tendon regeneration.
Thank You

Fact 2: Chimps have 90% gene makeup of a hip surgeon...is that true?

Just take a look at your knuckles....
References


