Smith-Lemli-Opitz Syndrome (SLOS) and the DHCR7 gene

Max Sellman

sellmangen564s14.weebly.com
What is SLOS?

Cholesterol metabolism disorder

Developmental and debilitating

Relatively common in populations of European origin
Morphological symptoms of SLOS

- 2/3 Toe Syndactyly
- Microcephaly
- Cleft Palate

Normal head size
Microcephaly
Biochemical Symptoms of SLOS

Failure to thrive

Mental retardation

Cholesterol deficiency

Buildup of cholesterol precursors

7DHC and 8DHC
Treatment and management of SLOS

No cure for SLOS

Cholesterol supplementation

Symptom control
DHCR7

7-dehydrocholesterol reductase

Last step in this cholesterol pathway
DHCR7 Gene Ontology

**Cellular Component**
- Intracellular membrane-bound organelle

**Molecular Function**
- 7-dehydrocholesterol activity

**Biological Process**
- Lung Development
- Regulation of cholesterol biosynthetic process
- Post-embryonic development
- Multicellular organism growth
- Cell differentiation
- Blood vessel development
- Regulation of cell proliferation
- Sterol biosynthetic process
DHCR7 is expressed in many cell types
DHCR7 is expressed in many cell types
DHCR7 is well conserved

- Human: 100% identical
- Chimpanzee: 99% identical, 99% similar
- Dog: 89% identical, 94% similar
- Cow: 89% identical, 93% similar
- House Mouse: 88% identical, 94% similar
- Norway Rat: 87% identical, 93% similar
- Red Junglefowl: 76% identical, 87% similar
- Zebrafish: 75% identical, 84% similar
- A. thaliana: 37% identical, 57% similar
- c.elegans: 29% identical, 45% similar
DHCR7 is well conserved

Human
Chimp
Mouse
Cow
Zebrafish
Arabidopsis

ERG4/ERG24- Ergosterol Biosynthesis
DHCR7 is well conserved

Human
Chimp
Mouse
Cow
Zebrafish
Arabidopsis

ERG4/ERG24- Ergosterol Biosynthesis
Transmembrane Domain
SLOS is caused by mutation in DHCR7
SLOS is caused by mutation in DHCR7
DHCR7 does not work alone
DHCR7 does not work alone

Sterol biosynthesis proteins
DHCR7 does not work alone!

Fatty-acid biosynthesis proteins
DHCR7 does not work alone!

SP1 is an important transcription factor.
What are the factors that contribute to the SLOS phenotype?

Cholesterol deficiency

Buildup of cholesterol precursors?

Other effects?
What are the factors that contribute to the SLOS phenotype?

- Cholesterol deficiency
- Buildup of cholesterol precursors?
- Other effects?

What else changes in the body as a result of a DHCR7 mutation?
**Hypothesis**: The cholesterol deficit and buildup of cholesterol precursors in DHCR7- mutant mouse cells creates a stressed physiological environment in which changes to protein interactions and transcription occur.
Specific Aims

Aim 1: To identify proteins that are over- or under-expressed in Dhcr7 mutant mice.

Aim 2: To determine conserved proteins that interact with DHCR7 across species.

Aim 3: To establish the regulatory effects of a Dhcr7 mutation on gene expression throughout the cholesterol pathway.
Specific Aims

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Dhcr7 mouse model
Identifying changes in expression in Dhcr7 mutant mice

Study brain, liver, and adrenal cells

Use SILAC approach to quantify proteins in sample

Compare healthy to SLOS tissues
Aim 1: Anticipated results

Impact on expression of proteins with GO term “cholesterol biosynthesis”

The unanticipated?
Specific Aims

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Determining conserved DHCR7 interactions

Query STRING for conserved interacting partners and complexes
Aim 2: Results

Human DHCR7

SP1
SREBF2

Associated Pathway Proteins
Aim 2: 
Results

Mouse Dhcr7

Sp1
Srebf1/2

Associated Pathway Proteins
Aim 2: Results

Zebrafish dhcr7

srebf1

Associated Pathway Proteins
Specific Aims

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Establishing the effects of a Dhcr7 mutation on pathway expression

Microarray experiments to generate expression datasets

Gene Set Enrichment Analysis to find affected pathways
Aim 3: Anticipated results and Future Directions

Some variance in pathway expression from wild type

Most DHCR7 mutations in humans have no model
References

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11. http://www.ohsu.edu/xd/health/services/doernbecher/research-education/research/research-labs/images/Stair_1.JPG


17. http://arrayit.com/rare_diseases.jsp


Cover Slide: http://www.bio.davidson.edu/projects/GCAT/tour/one_grid.jpg
Have a question?
Not sure what to feed your new pet?
Or what that strange weed is in your backyard?

ASK MAX!

From dogs to hogs,
And seeds to weeds,
Max has all the answers you need!