Liver Group 3

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General Strategy Outline

1. Generate a list of “interesting genes”
    a. p=0.05
2. Look for transcription factors
    a. Script to assign GO terms
    b. Manual assignment of GO terms
3. Map our interesting genes to KEGG pathways
    a. Over represented pathways
    b. Supervised clustering with genes from over represented pathways

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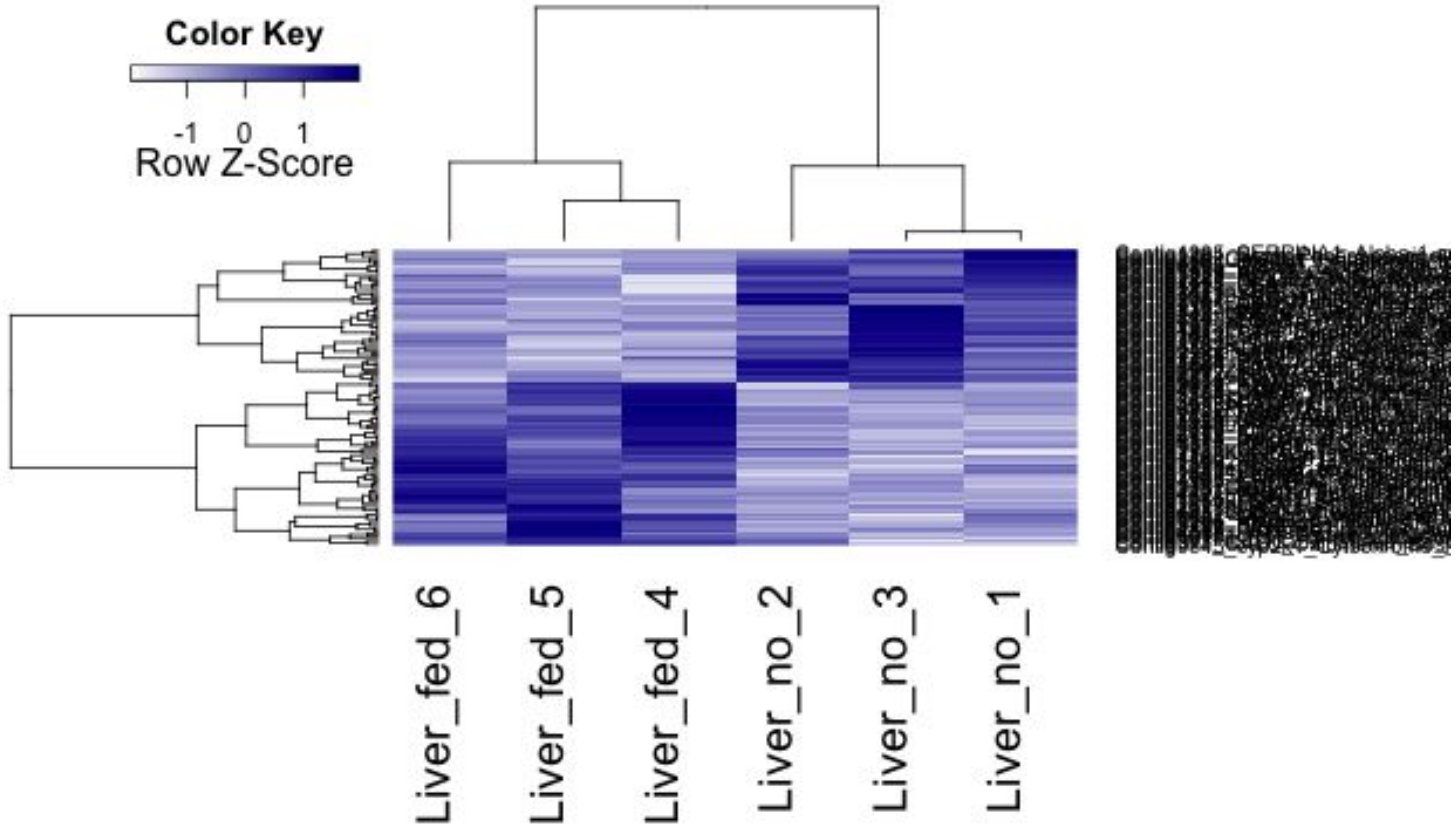
Generated a list of 110 differentially expressed genes between fed and unfed (p=0.05)



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Transcription Factors

- Of 110 differentially expressed genes, 49 assigned GO terms
  - 2 transcription factors
- Manually assigned GO terms to remaining 61 genes
  - 6 additional transcription factors
- **8 total transcription factors**

Transcription Factors

- ***SUB1*** - upregulated
  - General coactivator
- ***ZNF180*** - upregulated
  - Transcriptional regulator
- ***ACTG2*** - downregulated
  - Involved in cell motility & maintenance of cytoskeleton
- ***ZFP161*** - downregulated
  - Promotes transcription of other TFs (cell growth repressors)
- ***MYBBP1A*** - upregulated
  - Suppresses circadian clock component *PER2*
    - PER2 regulates physiological processes, including metabolism, based on circadian rhythms

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KEGG Pathways

01200 Carbon metabolism (1)
01212 Fatty acid metabolism (1)
01230 Biosynthesis of amino acids (2)
00680 Methane metabolism (1)
00061 Fatty acid biosynthesis (1)
00071 Fatty acid degradation (1)
00100 Steroid biosynthesis (1)
00561 Glycerolipid metabolism (1)
00564 Glycerophospholipid metabolism (1)
00230 Purine metabolism (1)
00240 Pyrimidine metabolism (1)
00260 Glycine, serine and threonine metabolism (2)
00270 Cysteine and methionine metabolism (2)
00310 Lysine degradation (1)
00380 Tryptophan metabolism (1)
00430 Taurine and hypotaurine metabolism (2)
00450 Selenocompound metabolism (1)
00460 Cyanoamino acid metabolism (1)
00480 Glutathione metabolism (1)
00533 Glycosaminoglycan biosynthesis - keratan sulfate (1)
00601 Glycosphingolipid biosynthesis - lacto and neolacto series (1)
00790 Folate biosynthesis (2)
00670 One carbon pool by folate (1)
00830 Retinol metabolism (2)
00900 Terpenoid backbone biosynthesis (1)
00909 Sesquiterpenoid and triterpenoid biosynthesis (1)
00362 Benzoate degradation (1)
00627 Aminobenzoate degradation (1)
03010 Ribosome (3)
04120 Ubiquitin mediated proteolysis (3)
03018 RNA degradation (1)
03410 Base excision repair (1)
02010 ABC transporters (1)
04014 Ras signaling pathway (1)
04015 Rap1 signaling pathway (1)
04010 MAPK signaling pathway (1)
04630 Jak-STAT signaling pathway (1)
04668 TNF signaling pathway (1)
04020 Calcium signaling pathway (2)

04024 cAMP signaling pathway (2)
04022 cGMP - PKG signaling pathway (1)
04151 PI3K-Akt signaling pathway (1)
04152 AMPK signaling pathway (1)
04080 Neuroactive ligand-receptor interaction (1)
04144 Endocytosis (2)
04142 Lysosome (3)
04110 Cell cycle (2)
04210 Apoptosis (3)
04510 Focal adhesion (1)
04540 Gap junction (1)
04610 Complement and coagulation cascades (2)
04611 Platelet activation (2)
04612 Antigen processing and presentation (1)
04910 Insulin signaling pathway (2)
04920 Adipocytokine signaling pathway (1)
04914 Progesterone-mediated oocyte maturation (1)
04917 Prolactin signaling pathway (1)
04918 Thyroid hormone synthesis (1)
04924 Renin secretion (1)
04925 Aldosterone synthesis and secretion (1)
04270 Vascular smooth muscle contraction (1)
04975 Fat digestion and absorption (1)
04728 Dopaminergic synapse (1)
04380 Osteoclast differentiation (1)
04212 Longevity regulating pathway - worm (2)
05200 Pathways in cancer (1)
05206 MicroRNAs in cancer (1)
05205 Proteoglycans in cancer (1)
05203 Viral carcinogenesis (1)
05212 Pancreatic cancer (1)
05214 Glioma (1)
05220 Chronic myeloid leukemia (1)
05218 Melanoma (1)
05222 Small cell lung cancer (1)
05223 Non-small cell lung cancer (1)
05323 Rheumatoid arthritis (1)
05340 Primary immunodeficiency (1)
05010 Alzheimer's disease (1)
05012 Parkinson's disease (2)

05014 Amyotrophic lateral sclerosis (ALS) (1)
05016 Huntington's disease (1)
05030 Cocaine addiction (1)
05031 Amphetamine addiction (1)
05034 Alcoholism (1)
04930 Type II diabetes mellitus (1)
04932 Non-alcoholic fatty liver disease (NAFLD) (1)
04931 Insulin resistance (1)
05130 Pathogenic Escherichia coli infection (1)
05132 Salmonella infection (1)
05131 Shigellosis (1)
05152 Tuberculosis (1)
05100 Bacterial invasion of epithelial cells (1)
05166 HTLV-I infection (1)
05162 Measles (2)
05164 Influenza A (2)
05161 Hepatitis B (1)
05160 Hepatitis C (1)
05168 Herpes simplex infection (1)
05169 Epstein-Barr virus infection (1)
05144 Malaria (1)

Pathways - what we found

1. Conducted literature search on overrepresented pathways
    a. Lysosome, ubiquitin mediated proteolysis, ribosome, apoptosis.
2. Genes of interest were then supervised cluster to determine whether any additional possible important genes were found.
3. A single gene of interest from the protein mediated proteolysis pathway stood out.

Lysosome
1. Cathepsin B
2. LAPTM
3. Saposin

UPM
1. Ubiquitin-conjugating E2B
2. **Suppressor of Cytokine Signaling 3**
3. Anaphase promoting complex 13

Ribosome
1. RP-LPO
2. RP-S24E
3. RP-L18Ae

Apoptosis
1. Cathepsin B
2. Alpha-Tubulin
3. Poly ADP-Ribose Polymerase

Suppressor of Cytokine Signaling 3 (SOC3)

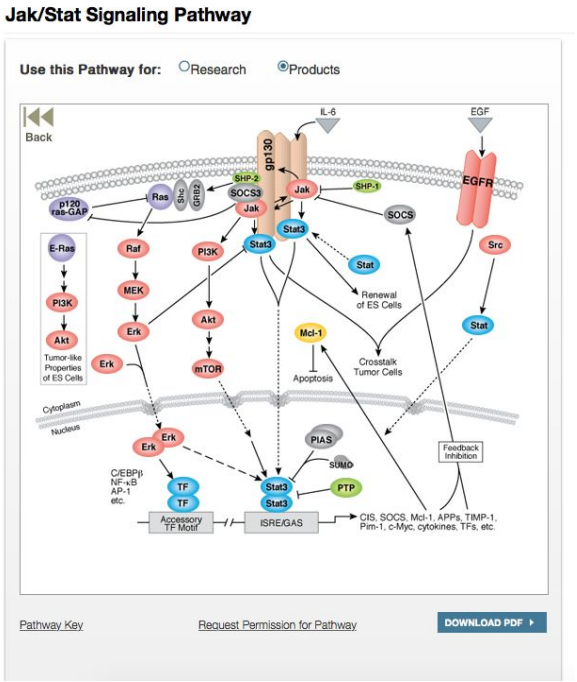
A negative feedback protein for the JAK/STAT pathway, acts on several levels. Prevents the ongoing activation of pathway.

JAK-STAT turned on by binding of cytokines or growth factors.

In liver, inhibits IL-6 signaling through gp130 receptor.

STAT3 enters nucleus and turns on transcription.

Post partial hepatectomy, innate immune system involved in initiating liver regeneration.



What could SOC3 Downregulation Mean?

In SOC3 knockout mice (hepatocyte-specific) undergoing partial hepatectomy = ENHANCED DNA synthesis and LIVER WEIGHT RESTORATION

Cytokine Activity Pathways Affected by SOC3 -/-

STAT3: increased

TLR: increased

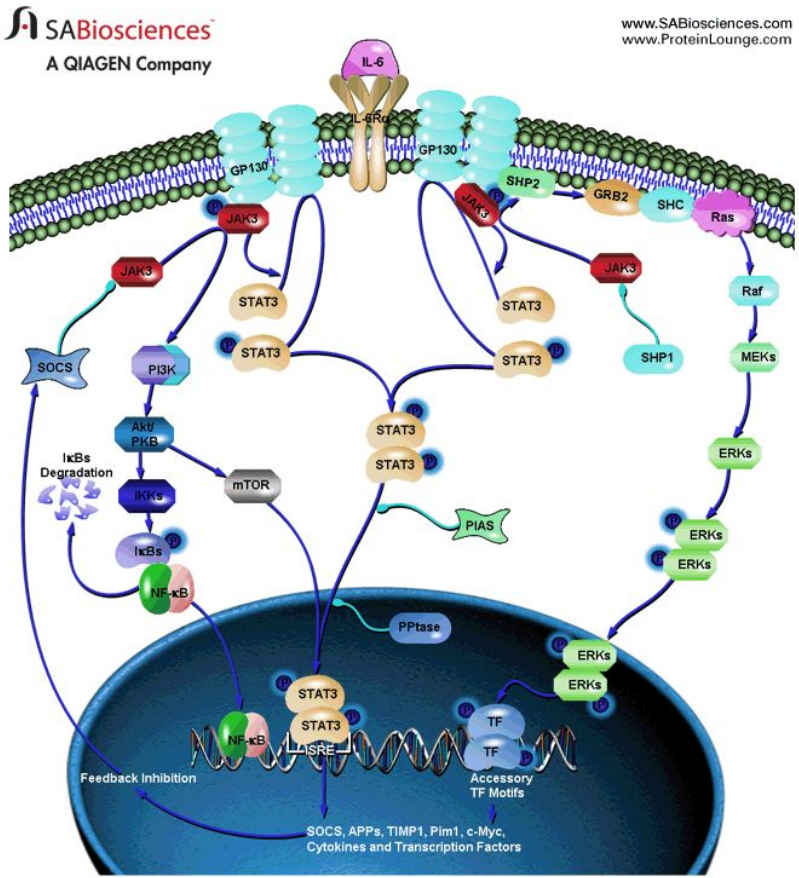
ERK: increased

TNF: activation prolonged

IL: activation prolonged

MAPK: activation prolonged

SOC3 may actually coordinate the response.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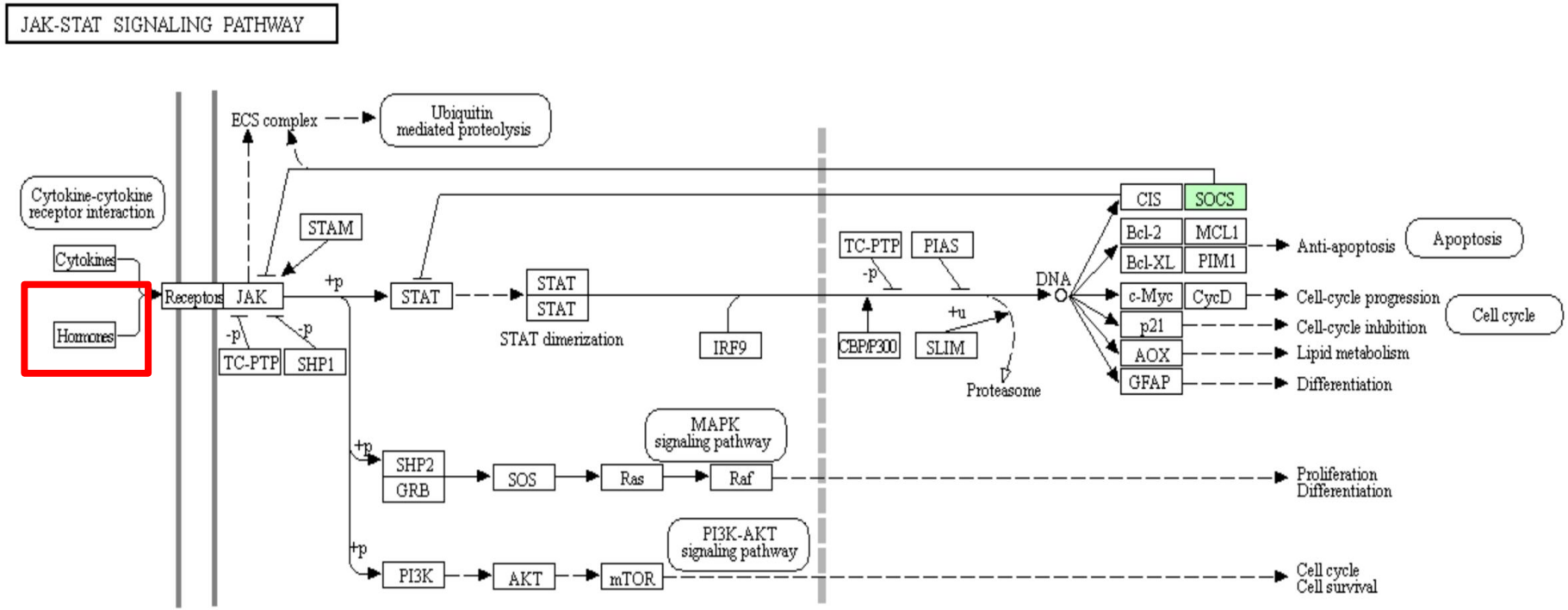
IL-6
IL-6Rα
GP130
GP130
JAK3
JAK3
JAK3
JAK3
JAK3
SHP2
GRB2
SHC
Ras
Raf
MEKs
ERKs
ERKs
ERKs
ERKs
SHP1
STAT3
STAT3
STAT3
STAT3
STAT3
STAT3
SOCS
PI3K
Akt/
PKB
mTOR
IκBs
Degradation
IKKs
IκBs
NF-κB
PIAS
PPtase
NF-κB
ISRE
TF
TF
Accessory
TF Motifs
Feedback Inhibition
SOCS, APPs, TIMP1, Pim1, c-Myc,
Cytokines and Transcription Factors

SOC3-related Transcription Factors

- ***CITED2*** - downregulated
  - Inhibits HIF-induced genes (HIF upregulated in SOCS3 KO)
    - Involved in angiogenesis, Associated with liver regeneration
- ***KDM6B*** - upregulated
  - Involved in inflammatory response via regulation of macrophage differentiation
  - Potential coactivator of HIF-α
- ***PARP1*** - upregulated
  - Component of NF-κB pathway
    - Inflammation-related pathway directly related to JAK-STAT pathway and regulated by SOCS

JAK-STAT pathway is hormone sensitive



JAK-STAT pathway is hormone sensitive

- Hormone sensitivity makes sense for rapid changes
- Potential candidates:
  - Epidermal growth factor
  - Ghrelin
  - Insulin
- Olfactory stimuli can affect hormone levels

Moving Forward

Map genes to KEGG with expanded p value

Look for JAK-STAT related genes

Sources

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3529618/

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3529618/

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