Gene expression analysis of mammary gland transdifferentiation

Characterisation of the data set:

(links given during text refer to web page: http://genome.tugraz.at/MammaryTD/)

Adipogenic markers (see 2.g.)

Classical markers of the adipogenic phenotype can be found in cluster 1 (down-regulated).

These include:

- Transcriptional regulators (such as Ppar γ, LXRα, Fgf10, Stat5a)
- Markers of mature adipocytes (such as Perilipin, Fabp4)
- Adipocytokines (such as Leptin, Tnf, Adipsin)
- Lipases (such as Hsl, Lpl, Mgl)
- Enzymes involved in triglyceride synthesis (such as Dgat1, Agpat2, Ppap2B, Fatty acid transporter)
- Enzymes involved in fatty acid synthesis (such as Fasn)

GO analyses show an over-representation of lipid-specific GO terms in cluster1 (see 4.a.). For example: lipid transport, lipid metabolism, fatty acid metabolism. Lipid metabolism is ranked highest in the GO mapping using only RefSeq IDs with an adjusted p-value of 0.0001 (highly significant, see 4.b.).

Taken together, this data confirms the pattern suggested by Anderson et. al. in their recent review [1] (Figure 3 and 7) and underpins the reduction of mammary adipocytes during pregnancy.

Mammary epithelial markers (see 2.g.)

Markers of late mammary epithelial development like Prolactin receptor (Prlr), milk fat globule-EGF factor 8 protein (Mfge8), Adipophilin (=Adfp), Muc-1, ATP citrate lyase and Glut-1 (=Slc2a1) were found to be up-regulated in the data set and confirmed the profiles stated by Anderson et. al [1]. Further, Ormandy et.al. established Prlr downstream genes by transcriptional profiling of tissues from

Prlr-/- to wild-type mice [2]. From this paper Keratins (Krt2-8, Krt1-19, Krt1-18) and Claudins (Cldn3, Cldn7), as well as the transcription factors Gata3 and Tcfap2c, emerge as markers for epithelial development, all of which are up-regulated in the data set. Classical milk proteins (caseins or whey acidic protein) are not in the data set because they are not spotted on the microarray. However, GO analyses suggest a massive up-regulation (predominantly in cluster 2; see 4.a.) in the protein biosynthesis and ribosomal biogenesis, which may indicate an increase in the milk protein production machinery. These GO terms are also significantly enriched in the data set (see 4.b.).

Patterns in data set:

Rudolph et.al. [3] show an overall down-regulation of Collagens during pregnancy. This is consistent with the regulation of Collagens contained in the data set (see 2.g. and 4.).

Most nuclear receptors contained in the data set are down-regulated. Notably, the two isoforms of LXR are regulated reciprocally (LXRα down, LXRβ up).

The same reciprocal profile can be seen for the Stat5 isoforms (Stat5a down, Stat5b up).

Further, significant enrichment for GO terms associated with extracellular matrix, endoplamatic reticulum, golgi, cell adhesion, positive regualtion of transcription, ribonucleoprotein and apoptosis could be shown. Immune and inflammatory response is mainly found in cluster 1 (see 4.a.).

Summary:

The initial analysis proofs that the experimental setup is biologically plausible, because of major overlaps with the current literature.

More detailed analysis and corrleation with protein data might reveal mechanisms and factors that induce the transdifferentiation of mammary adipocytes into mammary epithelial cells.

Reference List

1. Anderson,S.M., Rudolph,M.C., McManaman,J.L. & Neville,M.C. Key stages in mammary gland development. Secretory activation in the mammary gland: it's not just about milk protein synthesis! Breast Cancer Res. 9, 204 (2007).

2. Ormandy,C.J. et al. Investigation of the transcriptional changes underlying functional defects in the mammary glands of prolactin receptor knockout mice. Recent Prog. Horm. Res. 58, 297-323 (2003).

3. Rudolph,M.C., McManaman,J.L., Hunter,L., Phang,T. & Neville,M.C. Functional development of the mammary gland: use of expression profiling and trajectory clustering to reveal changes in gene expression during pregnancy, lactation, and involution. J Mammary. Gland. Biol. Neoplasia. 8, 287-307 (2003).