Glycogen metabolism and Cori cycle in human hair follicles

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BACKGROUND

The **hair follicle (HF)** is a dynamic mini-organ that continuously undergoes phases of growth (anagen), apoptosis-driven regression (catagen), and relative quiescence (telogen).

Hair follicles have one of the highest rates of cell division in the human body and metabolise 90% of glucose to lactate. Catabolism of glucose to lactate is considered energetically inefficient, but in actively proliferating cells catabolism of glucose to lactate generates a high flux of metabolites that can be tapped for biosynthesis of proteins, nucleic acids and lipids and thus contribute to biomass and growth control.

Cori cycle is a metabolic process mainly occurring in the liver, in which excess lactate is converted into glucose through gluconeogenesis to prevent lactic acidosis. Glucose is then used for glycogen replenishment.

Glycogen is osmotically neutral glucose polymer found mostly in the liver and skeletal muscle, but also in hair follicles.

The aim of this study is to determine the presence and localisation of glycogen and glycogen metabolism enzymes in human hair follicles and to dissect the possibility of the Cori cycle operating in the hair follicle.

RESULTS

1 Glycogen is present in the ORS of human hair follicles

Figure 1 Glycogen presence: Periodic Acid Schiff staining (magenta glycogen staining) in (A)-human scalp section; B-E-isolated anagen hair follicles from the bulb (B), suprabulbar region (C, D) and bulge region (E). (F)-staining intensity quantification in anagen and catagen hair follicles (**** $P < 0.0001$). (G)-PAS staining in catagen hair follicle (cultured in vitro for 5 days). Scalp skin sections with telogen (H) and early anagen (I) hair follicles. Liver sections stained for glycogen as a positive control (J); (K)-negative control (digestion with α -amylase from porcine pancreas) in the liver and in scalp skin section (L).

2 Glucose transporter 1 is expressed in the ORS

Figure 2 Expression of glucose transporter 1 (Glut1) (A)-immunofluorescence staining quantification in the ORS in anagen and catagen hair follicles, (B)-relative mRNA expression of Glut1 in anagen and catagen hair follicles (n=2), normalised to B2M, n.s. $p > 0.05$. Immunofluorescence performed in isolated anagen (C) and catagen (D, cultured in vitro for six days) hair follicles using anti Glut1 rabbit antibody and secondary goat anti rabbit antibody (Alexa Fluor 488), blue nuclear staining obtained with DAPI. Scale bars denote 100 μ m.

3 Glycogen synthase 1 is expressed in the IRS and basal ORS

Figure 3 Expression glycogen synthase 1 (GYS1) Immunofluorescence performed in isolated anagen (A) and catagen (B, cultured in vitro for six days) hair follicles using anti GYS1 rabbit antibody and secondary goat anti rabbit antibody (Alexa Fluor 488), blue nuclear staining obtained with DAPI. (C)-digital focus of anagen hair bulb with Flügel cells labelled with arrows. Scale bars denote 100 μ m. (D)-relative mRNA expression of GYS1 in anagen and catagen hair follicles (n=2), normalised to B2M, n.s. $p > 0.05$.

4 Glycogen phosphorylase is expressed in the ORS

Figure 4 Expression of glycogen phosphorylase (PYGL) (A)-staining quantification in the ORS in anagen and catagen hair follicles, (B)-relative mRNA expression of PYGL in anagen and catagen hair follicles (n=2), normalised to B2M, * $p < 0.05$. Immunofluorescence performed in isolated anagen (C) and catagen (D, cultured in vitro for six days) hair follicles using anti Glut1 rabbit antibody and secondary goat anti rabbit antibody (Alexa Fluor 488), blue nuclear staining obtained with DAPI. Scale bars denote 100 μ m.

5 Phosphoglucomutase 1 presents the strongest expression in the cuticle

Figure 5 Expression of phosphoglucomutase 1 (PGM1) Immunofluorescence performed in isolated anagen (A) and catagen (B, cultured in vitro for six days) hair follicles using anti PGM1 rabbit antibody and secondary goat anti rabbit antibody (Alexa Fluor 488), blue nuclear staining obtained with DAPI. (C)-zoomed image of suprabulbar region stained with PGM1 and LDHA. (D)-relative mRNA expression of PGM1 in anagen and catagen hair follicles (n=2), normalised to B2M, n.s. $p > 0.05$.

6 ORS keratinocytes are capable of the Cori cycle

Figure 6 Functional tests of Cori cycle (A)-Western Blot analysis of ORS keratinocytes with induced lactic acidosis with glycogen depletion and without starvation. (B)-quantitative glycogen assay in ORS keratinocytes with depleted glycogen and induced lactic acidosis and without starvation (C). Immunofluorescence performed in isolated anagen (D) and catagen (E, cultured in vitro for six days) hair follicles using anti PCK1 antibody Scale bars denote 100 μ m. (F)-quantification of PCK1 staining intensity in the ORS of anagen and catagen hair follicles.

CONCLUSIONS

- Hair follicles contain high amounts of glycogen
- Glycogen level changes with hair follicle growth phases
- Glycogen metabolism enzymes present distinct expression patterns in hair follicles
- Glycogen-source of energy, precursors for keratinisation?**
- Hair follicles express crucial gluconeogenetic enzyme-PCK1
- Do ORS keratinocytes produce glycogen to prevent lactic acidosis?
- Is hair follicle the liver of the skin?**