Metformin directly alters key glycolytic enzyme protein expression and mitochondrial function in the endometria of PCOS patients

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Background and Purpose

In a recent case study, we have reported a proof-of-concept that a combination of metformin and oral contraceptives treats early-stage endometrial cancer (EC) in women with polycystic ovary syndrome (PCOS). Although metformin-induced metabolic effects in PCOS patients have been investigated, it is not known whether this therapeutic drug has a direct effect on the endometria and further regulates glycolysis and mitochondrial function in PCOS patients with endometrial hyperplasia and carcinoma.

Results

1. Endometria from PCOS patients with endometrial hyperplasia and carcinoma have a distinct protein expression pattern of glycolytic enzymes (Fig. 1A), including HK2, PFK, PKM2, and LDHA as well as mitochondrial TFAM, which is necessary for energy production from oxidative phosphorylation (Fig. 1B).

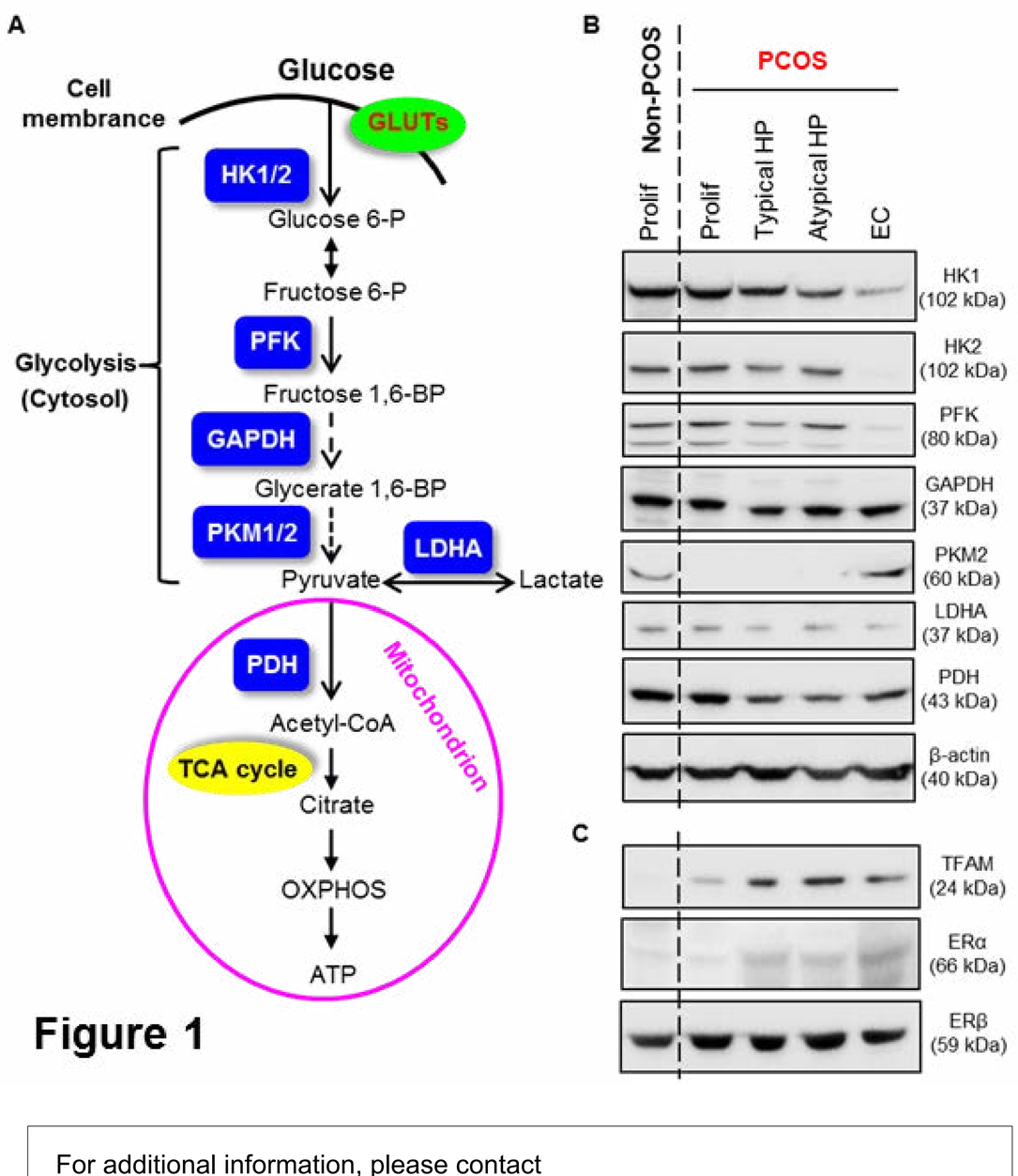

Figure 1

Conclusions

Our data indicate that metformin integrates endometrial glycolytic metabolism with mitochondria-related cellular function by direct regulating key glycolytic enzyme protein expression in the endometrium. Our results also show that ERα is a molecular link between metformin action and estrogen-induced endometrial cell proliferation, and they shed further light on the anticancer mechanism of metformin in PCOS patients with EC.

2. Using endometrial tissues from PCOS patients with hyperplasia, we evaluated the effects of metformin on the protein levels of key enzymes in glycolysis in vitro. In response to metformin (20 mM) treatment, HK2 expression was decreased, whereas PFK, PKM2, and LDHA expression was increased compared to controls (Fig. 2A). Interestingly, the expression of TFAM and cleaved caspase-3, a downstream target of cytochrome C, was increased after metformin treatment (Fig.2B).

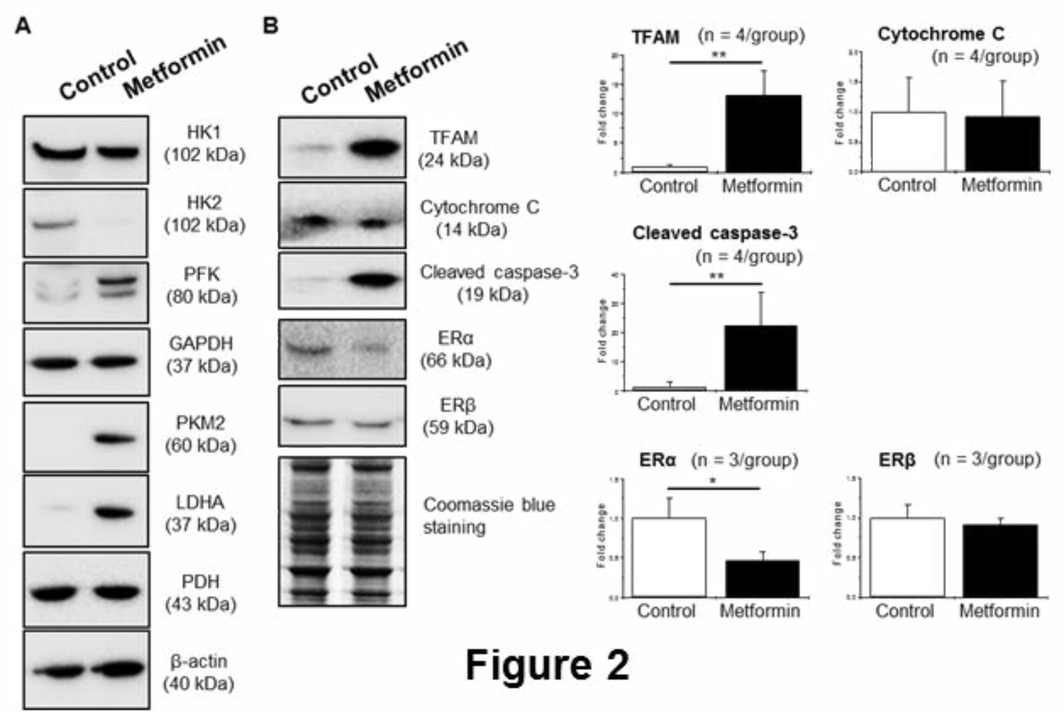

Figure 2

3. While endometrial ERβ expression was no different between non-PCOS and PCOS patients, ERα expression was gradually increased in women with PCOS following the onset of endometrial hyperplasia and carcinoma (Fig. 1C). Moreover, we found that in vitro treatment with 20 mM metformin leads to inhibition of ERα expression without affecting ERβ expression (Fig. 2B).

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