

## Lecture 22

### Urea Cycle, Gluconeogenesis and Glyoxalate Cycle

**1. Why is it necessary that the first steps of the urea cycle take place in the mitochondria?**

**Answer:** FK: This allows the existence of two isoforms of carbamoyl phosphate synthetase (CPS). The mitochondrial isoenzymes CPS I uses free ammonia as nitrogen source, and is (positively) allosterically controlled by N-acetyl glutamate (the product of the first step in the biosynthesis of ornithine). The cytosolic isoforms CPS II utilises glutamine as nitrogen source. These enzyme catalyses the first step in pyrimidine biosynthesis (and also of arginine biosynthesis) and is controlled by phosphorylation (MAP kinase pathway). So independent control of nucleotide biosynthesis and amino acid degradation, respectively, is possible.

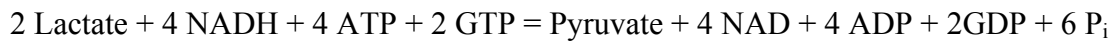
**2. Are the urea cycle and the TCA cycle run at the same time, since they use the same intermediates?**

**Answer:** Since the urea cycle just uses a part of the TCA cycle to regenerate aspartate, so this does not require “running” of the cycle and could even be accomplished in the total absence of acetyl-CoA. But you’re right, oxaloacetate has several possible fates (condensation with acetyl-CoA, transamination, gluconeogenesis), and thus there might be something like a “competition” between TCA and urea cycles. The urea cycle is largely controlled by substrate availability,  $\text{NH}_3$  and glutamate being the most important factors. If there is enough glutamate,

NH<sub>3</sub> will be produced (by glutamate dehydrogenase), N-acetyl glutamate will be synthesised (the first step of ornithine biosynthesis, and also an allosteric activator of carbamoyl phosphate synthetase), and transamination of oxaloacetate will be more likely than alternative reactions.

**3. Calculate the number of ATP equivalents required to synthesize 1 molecule of glucose from 2 molecules of lactate via gluconeogenesis?**

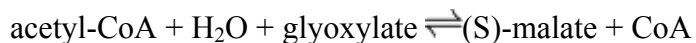
**Answer:** The net reaction of gluconeogenesis



The total number of ATP required is 18 (4 x 3 + 4 + 2).

**4. One reaction of the glyoxylate cycle is formally analogous to the reaction catalyzed by citrate synthase of the Krebs cycle. Write the reaction of the glyoxylate cycle using structures and abbreviations for co-factors.**

**Answer:** Glyoxylate condenses with acetyl-CoA (a step catalyzed by malate synthase), yielding malate. This is formally analogous to the reaction catalyzed by citrate synthase of the Krebs cycle.



The 3 substrates of this enzyme are acetyl-CoA, H<sub>2</sub>O, and glyoxylate, whereas its two products are (S)-malate and CoA.

**5. An enzyme used in both glycolysis and gluconeogenesis is:**

**Answer:** a) 3-phosphoglycerate kinase.