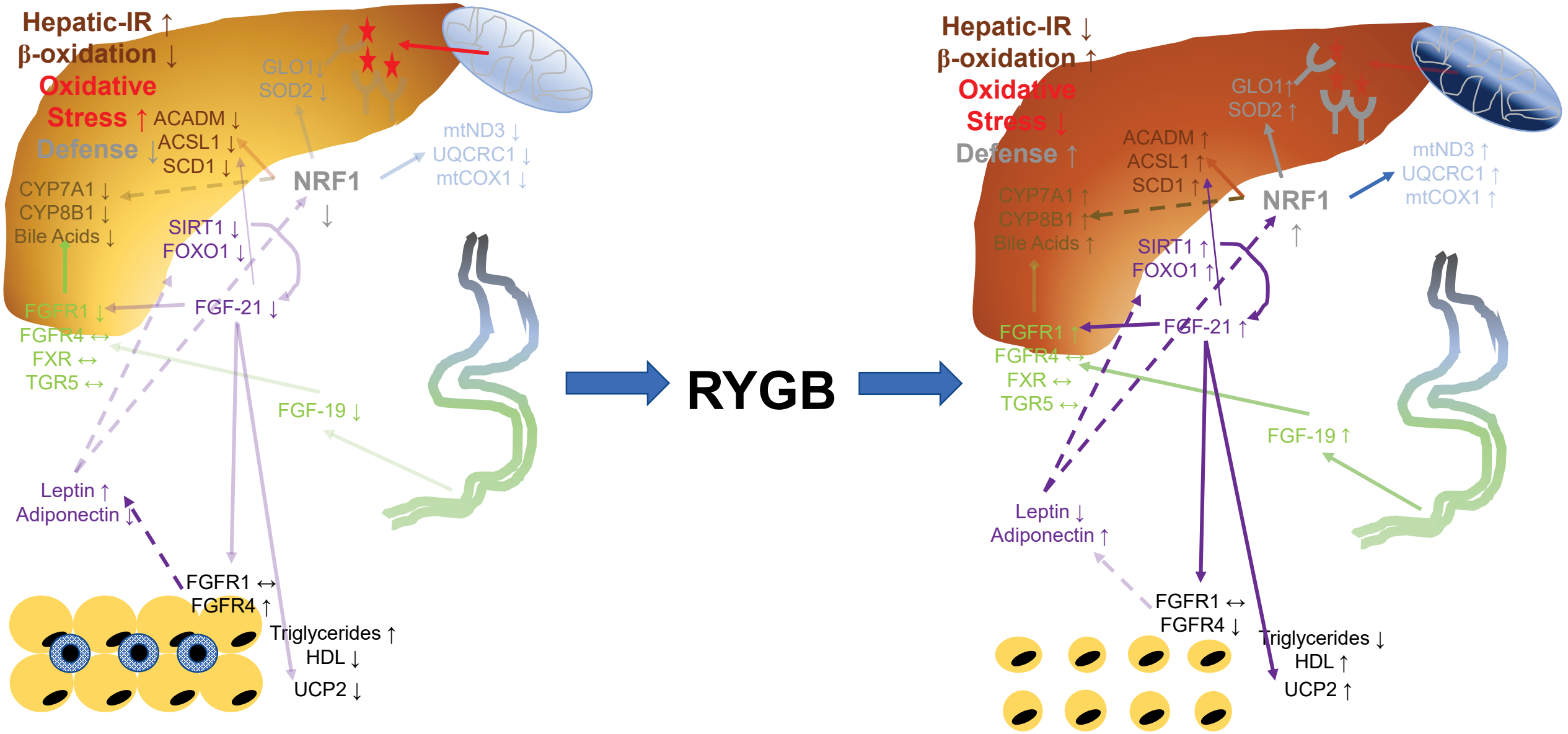
Supplementary Figure 3



Legend Supplementary Figure 3

- **Figure 5: Proposed Mechanisms of MAFLD-resolution by RYGB**
- The red stars indicate oxidative stress which is high in MAFLD due to low defense genes and mitochondrial dysfunction (blue). The main reason for that is likely a low NRF1 expression. Brown demonstrates the increased hepatic insulin resistance and the reduced β-oxidation in MAFLD and the genes indicative of this state. Green shows the relation of gut hormones and hepatic bile metabolism which is also suppressed in MAFLD. Purple shows the interaction of FGF-21, which is produced in the liver, and has beneficial effects on adipose tissue function as assessed by leptin and adiponectin. The different change on the receptors for FGF-19 and -21 in the liver and adipose tissue are also highlighted.
- RYGB reverses essentially all of these changes, most likely due to the upregulation of NRF1 which in turn upregulates the defense genes and restores mitochondria function as well as β-oxidation (highlighted by the bold arrows from NRF1). The upregulation of SIRT1, of which it is unclear through which mechanism, induces the transcription and secretion of FOXO1 and FGF-21 which in turn improve hepatic insulin resistance and hepatic metabolism. FGF-21 also acts in the adipose tissue and increases adiponectin which in turn exerts beneficial effects on the liver and other organs such as the kidney itself while leptin is suppressed. FGF-21 has also been implied to induce browning/beiging of the adipose tissue as indicated by UCP2. FGF-19 is upregulated through the increased in bile acids in the terminal ileum. However, the effects that are associated with increased FGF-19 such as the suppression of bile acid synthesis (CYP7A1 and CYP8B1) is not observed. This may be explained by the lack of expression change of FGFR4 which is the FGF-receptor that affects bile acid metabolism. However, FGF-19 also has beneficial effects on the hepatic metabolism which may be exerted through FGFR-1 which is upregulated after RYGB.