Towards the mechanism of early-life programming
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CHAPTER 7

SUMMARIZING DISCUSSION & CONCLUSION
DISCUSSION

The alarming increase in the prevalence of the metabolic syndrome in the western world but also in developing countries, can in part be contributed to the change in dietary habits and the lack of exercise. However, animal and epidemiological studies have indicated that nutrition during the fetal and/or the neonatal period also affects adult health. This concept has emerged in to the predictive adaptive response hypothesis, as postulated by Gluckman [214]. Predictive adaptive response describes the processes by which environmental interactions in early development lead to changes in the physiological phenotype of the developing fetus in expectation of future advantage in a particular predicted adult environment. A mismatch in this environment could predispose to or increase the vulnerability to develop certain metabolic diseases at later age.

In this thesis we characterized the physiological consequences of a maternal western diet during early developmental phases on the long-term health of the offspring. By doing this at several stages of development we aimed to elucidate part of the mechanism(s) that facilitates maternal programming.

In chapter 2 we presented the nutritional mouse model used to investigate the effect of maternal nutritional programming. The combination of maternal and offspring western diet feeding resulted in increased weight gain, hepatic hyperlipidemia as well as increased liver injury in the male offspring exclusively. This phenotype was confirmed by histopathological characterization and verification by hepatic expression of inflammatory markers. With this clear disease state in the adult male offspring we decided to concentrate on possible changes in the liver in the early period to investigate metabolic pathways vulnerable for programming (chapter 3). In two-week-old offspring of these dams, once again exclusively male offspring had significantly higher body weight upon maternal western diet compared with offspring from maternal control diet. Although this time, female liver to body weight ratio was also affected by maternal western diet, meaning an increase in liver weight compared to body weight. In addition blood parameters as well as hepatic gene expression profiles were changed in offspring of western diet-fed dams. Contrary to what one might expect from the long term results, the strongest regulated biological functions in males included cell developmental functions, whilst in females especially functions that relate to metabolism and energy homeostasis were among the highest regulated functions.

The second part of this thesis focused on the mechanisms facilitating maternal programming and sex specificity. In chapter 4 we performed histology on the placentas from offspring of the animal model used in this thesis. Although no difference was seen between the different maternal diets, there was a difference between the genders. We saw a distinct increase in the ratio between the labyrinth layer and the spongiotrophoblast layer for the male offspring only. This finding could indicate that the male placenta is being more apt to transport excess maternal nutrients to
the male fetus, whereas the placenta of the females acts as a barrier; consequently leading to increased growth in the male fetus in contrast to the female fetus.

In the last two experimental chapters of this thesis we investigated DNA methylation in and during development. In Chapter 5 we studied epigenetic DNA methylation as a mechanism that might facilitate programming effects to persist into adulthood. We had hypothesized to find early epigenetic marks that were conserved into adulthood possibly being able to serve as a marker for predisposition to develop liver disease. This proved to be more complex than anticipated. Although we did find a core set of offspring NAFLD specific methylation patterns was found to be corresponding to human steatohepatitis.

Identifying markers for a disease state is never easy, since rarely there is only one factor playing a role in determining the development of the fetus. The influence of maternal life-style in human programming is expected to be even more complex. In chapter 6 we have investigated if altered methylation patterns of genes in small for gestational age postpartum placentas are also present in placenta tissue obtained by chorionic villous biopsies from small for gestational age neonates. This early placental material is difficult to come by and therefore very valuable. Methylation changes found in late placenta could not be traced back to the early placenta samples, implying that these marks do not have a causative relation with the small for gestational age development.

Most of the findings in this thesis are in line with hypotheses in the literature proposing that prenatal exposure to a high caloric diet renders offspring especially sensitive to lipotoxic effects of postnatal high caloric diets. Murine models have consistently described lipid abnormalities in adult offspring exposed to a high fat diet during early phases of development [16-19,24,26,54,55,60]. In contrast to these studies, we have not been able to generate obese or insulin resistant dams when given obesogenic diets. In our studies an experimental high fat semi-synthetic diet was compared to a control semi-synthetic diet whereas in earlier studies obesogenic diets have been compared to rodent chow, which we regard as a flaw in experimental design. Despite this difference, we were able to show that maternal western diet predisposes to metabolic derangement in offspring adulthood.

Studies investigating the early phenotype of offspring by maternal programming report changes in lipogenic pathways similar to our results. Non-human primates of overnurished mothers show signs of NAFLD in the early third trimester [29]. In a rodent model of maternal over nutrition there was a liver to body weight difference, in addition enlarged hepatocytes and lipid accumulation in livers of offspring were observed [22]. However only few of the studies investigating the early effects of maternal programming reported on possible sex differences that could be present. Only scarce literature investigates placentation in the context of programming but, whenever it is done, most of these studies do focus on the sexually dimorphic placenta [39-41]. In terms of the human placenta, several studies have identified a number of differences in gene expression [215,216]. O’Connell et al. have shown that
the placenta exhibits sexually dimorphic placental development over time. Although
the study of O’Connell et al. did not investigate the effect of maternal nutrition, it does
strengthen our hypothesis that males are more vulnerable to a sub-optimal in utero
environment [132]. They hypothesized that the female feto-placental unit relies on
continued growth of vascular elements in the placenta throughout gestation, whereas
in the male feto-placental unit high fetal growth depends more heavily on the growth
of tissue containing transporter molecules.

This thesis has provided evidence of a substantial effect of diet during pregnancy
on both physiology and gene expression in rodent offspring at different stages of
development.

In the experiments performed in this thesis we have not been able to investigate
functional changes in addition to the molecular changes in this maternal nutritional
model. Future studies should investigate if the fetal and adult hepatic expression
levels of genes involved in lipid metabolism are translated into quantitative
changes in physiological relevant lipid fluxes. Indeed, several studies report that
liver functionality is affected by maternal malnutrition in the adult offspring, e.g.
gluconeogenesis, glucose handling, mitochondrial electron transport and phagocytic
function [18,20,26,217].

Future research should focus on finding early markers of the metabolic syndrome
leading to the development of comorbidities. In this frame sex specificity should
always be taken into account. In addition histone modifications and DNA methylation
patterns should be investigated in a gender specific manner.