Metabolic memories

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APPENDICES

References
Summary
Acknowledgments
List of publications

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SUMMARY

The development of an organism is determined both by its genetics and its environment. During early critical periods in life the organism has the flexibility to adapt to unphysiological genetic and/or environmental stimuli, by evoking adjustments at the molecular, cellular and systemic levels. Such early adaptations to genetic, nutritional or other environmental stressors can permanently change the physiology of the organism to an altered metabolic state, which persists or (re)appears in adulthood, even in the absence of the initiating stimulus. This process is broadly known as "metabolic programming". The changes in the structure and physiology of the fetus or neonate might later become disadvantageous resulting in increased risk for chronic disease. Some of the most prominent epidemiological observations link early life under- and malnutrition with adult obesity, type II diabetes, and dyslipidemia, which are main risk factors for death from coronary heart disease. Maintained changes in the epigenetic makeup of the young organism that influence the life-long expression pattern of genetic networks governing metabolism are often implicated in models of suboptimal nutrition, hormonal imbalances or environmental exposures. While the mechanisms guiding metabolic programming processes are still poorly understood, the interaction of genetic, environmental and epigenetic factors appears to be crucial for determining the balance between adult health and disease.

The aim of this work was to increase our current understanding of the factors and mechanisms driving early life metabolic programming. This thesis specifically addressed the role of fetal oxidative stress and of dietary cholesterol in the postnatal period for the susceptibility to cardiometabolic disease in adulthood. **Chapter 1** describes the current understanding of the metabolic programming phenomena, conserning oxidative stress and cholesterol homeostasis, as a background for the experimental chapters.

Oxidative stress is a crucial driver of tissue differentiation during fetal development, while in adulthood it emerges as an important component of the pathophysiology of cardiometabolic disease and obesity. It is also a common factor in many models of developmental programming. Its independent pathophysiological contribution, however, is experimentally difficult to assess. Research described in **Chapter 2** addressed the effects of isolated intrauterine oxidative stress on adiposity, glucose and cholesterol metabolism in adult offspring of *Sod2+/- Ldlr -/-* mice challenged with Western diet. Mice previously exposed to oxidative fetal environment remained leaner, with higher glucose tolerance and more efficient cholesterol clearance from the circulation. The response was present only in male offspring, indicating sexual dimorphism. Further identified was increased expression of the uncoupling protein 1 (UCP1) in white adipose tissue, a hallmark of so

called "browning"of white adipose tissue, as potential mechanism for the lower adiposity of the group. The protective effect of fetal oxidative stress exposure against the detrimental effects of Western diet resonates with the mitohormesis theory. In agreement with it, our data suggest that fetal oxidative stress provides biological resistance toward the adverse effects of larger successive doses of it, i.e. oxidative stress associated with Western diet regimen. By extending the mitohormesis concept into the field of metabolic programming the results in **Chapter 2** stimulate rethinking the idea of invariably adverse impact of early life stressors on programming of adult metabolism. It is likely that the physiological outcome is determined as much by adult context as it is by early life conditions.

Besides fetal development, the postnatal developmental window presents opportunities for persistent epigenetic and metabolic adaptations in response to early life nutrition to take place. The cholesterol content of breast milk has been hypothesized to be important for both immediate and long-term health of the offspring. **Chapter 3** investigated the mechanisms for regulation of the cholesterol content of milk by focusing on the relationship between maternal hypercholesterolemia and milk cholesterol levels. Our results demonstrate that milk cholesterol content is maintained stable under varying degrees of hypocholesterolemia, and is also independent from the expression of Abcg8 or Ldlr. The robustness of the milk cholesterol content supports the idea for an important physiological function.

Epidemiological observations link breastfeeding with lower cardiometabolic disease risk in adulthood. Hypothetically the cholesterol content of breast milk plays a role in determining key parameters of adult cholesterol metabolism. **Chapter 5** investigated the consequences of decreased milk cholesterol availability from milk, early in life, on metabolism of cholesterol in adult Ldlr knockout mice. By administering the cholesterol absorption inhibitor ezetimibe via the dams's milk to newborn mice, bioavailability of cholesterol from milk in the pups was reduced. After weaning at three weeks of age, cholesterol absorption remained decreased in the young offspring, associated with lower total plasma and V(LDL) cholesterol levels, similar to the situation of infants fed cholesterol-free formula. At the time of weaning, the gene expression of the main intestinal cholesterol transporter NPC1L1 was not affected in post-ezetimibe mice. In contrast, at 24 weeks of age both gene and protein levels were downregulated which was accompanied by significantly lower cholesterol absorption rates in the group. Increased histone H3K9me3 methylation, an chromatin modification associated with gene silencing, in the promoter-proximal region of NPC1L1, was identified as plausible mechanism. Together, these data demonstrate for the first time the ability of the mammalian intestine to establish and maintain an active metabolic memory of early life nutritional challenges by evoking epigenetic modifications of genes. No differences in plasma cholesterol levels

or atherosclerotic plaque size were observed between the groups. Although this model does not explain the plasma cholesterol lowering effect of breastfeeding seen in human, it provides valuable insights that could possibly aid the development of novel cholesterol lowering strategies.

Western diets which contain both high-fat and high cholesterol, but also diets with exclusively high-fat content elicit shifts in the composition of intestinal microbiota with a strong contribution to the adverse metabolic effects of the diets. High amounts of dietary cholesterol increase the pro-atherogenic plasma cholesterol and associate with a number of (patho)physiological changes. **Chapter 4** explored whether some of these changes may be conveyed indirectly by the impact of dietary cholesterol on the composition and function of gut microbiota. Our data demonstrated that in adult *Ldlr*-knockout mice high cholesterol diet alone does not introduce major shifts in microbiota composition despite inducing substantial adaptive response in whole body cholesterol homeostasis of the host. These results imply that the strong impact of Western diet on intestinal microbiota is likely to be mediated exclusively by its high-fat content, and not by its cholesterol content. A future research direction could be to evaluate whether dietary cholesterol does play a role in the establishment of the intestinal microflora in the early days after birth when colonization takes place.

Overall, the research described in this thesis provides valuable new insights into the complexity of mechanisms involved in programming of adult metabolism by early life exposures. The described results emphasize the importance of intrauterine oxidative stress and cholesterol in early postnatal development and its ability to induce long-term modifications in the epigenetic makeup of the organism. Future research would need to target the identification of epigenetically active nutrient sensors, which translate environmental conditions into altered gene expression conveying the adaptive physiologic response into adulthood. Further increasing our insights into the mechanisms of programming could open possibilities for preventive or therapeutical interventions in early life, to set the stage for long-term healthy ageing.

АКАДЕМИЧНО РЕЗЮМЕ

Развитието на организма се определя главно от неговата генетика. Въпреки това, по време на ранните критични периоди от живота, многоклетъчният организъм е способен да реагира на стимули, чужди на неговото нормално равитие, които предизвикват адаптации на молекулярно, клетъчно и системно равнище. Такива ранни адаптации към стресори от хранителната или околна среда, могат перманентно да променят физиологията на организма, при което промените в метаболизма му се запазват в напреднала възраст дори при отсъствие на иницииращите стимули. Този процес е известен като метаболитно програмиране. Промените в структурите и физиологията на плода или новороденото е възможно в по-късна възраст да станат неизгодни и да предразположат към повишен риск от хронични заболявания. Някои от най-емблематичните епидемиологични изследвания свързват ранното недохранване с отключване на компесаторни механизми и по-късно развитие на затлъстяване, диабет II-ри тип и хиперлипидемия, които са главните рискови фактори за смърт от коронарна болест на сърцето. Промени в епигенетиката на младия организъм, които влияят на доживотната експресия на генетичните мрежи, регулиращи метаболизма, са често срещан феномен в моделите на фетално недохранване, хормонален дисбаланс или излагане на елементи от средата. Въпреки, че механизмите направляващи процесите на метаболитно програмиране са все още слабо разбрани, взаимодействието между генетични и епиегенетични фактори с фактори от средата се оказва предначертаващо за баланса между здраве и болести в напреднала възраст. Целта на изследванията, описани в тази дисертация, е да разшири настоящето разбиране за факторите и механизмите, явяващи се двигатели на метаболитно програмиране в ранна възраст. Специално внимание е обърнато на феталния оксидативен стрес и холестерола, приеман с кърмата в ранния постнатален период и ролята, която те играят за развитието на предразположеност към сърдечно-съдови и метаболитни заболявания в по-късния етап от живота.

Окислителния стрес е основен двигател на тъканната диференциация по време на феталното развитие, докато във възрастния организъм се проявява като важен компонент от патофиозиологията на затлъстяването и атеросклерозата. Също така е често срещан фактор при множество модели на метаболитно програмиране. Неговият независим патофизиологичен принос към тези процеси обаче е експериментално труден за оценка. В Глава 2 е адресиран ефекта от изолацията на феталния оксидативен стрес по отношение на нивото на затлъстялост, и промени в метаболизма на глюкозата и холестерола. Избраният експериментален модел използва хранително предизвикателство с високо мастна и холестеролова,

"западна" диета, предоставена на мишки, произлезли от майки с генотип Sod2+/- *Ldlr* -/-, придружен от улеличена продукция на свободни радикали в плацентата. В зрелост, мишките, предварително изложени на окислителна фетална среда, остават по-слаби, с висока глюкозна толерантност и по-ефективно изчистване на холестерол от кръвообръщението. Ефектът е полово-диморфен и е налице само при мъжкото поколение. Индентифицирана е повишената експресия на uncoupling protein 1 (UCP1) в бяла мастна тъкан като вероятен механизъм, на който се дължи по-ниското ниво на затлъстялост в групата. Защитният ефект от излагането на фетален окислителен стрес е в синхрон с теорията за митохормезата. Съгласно нея, резултатите тук предлагат идеята, че феталният окислителен стрес осигурява биологична резистентност към негативните ефекти асоциирани с по-големи последващи дози окислителен стресс, каквито са асоциирани със западния хранителен режим. Прехвърляйки принципите на митохормезата в полето на метаболитното програмиране, резултатите от Глава 2 предполагат преобмисляне на идеята за неизменно негативен ефект от излагането на стесови фактори в ранния живот.

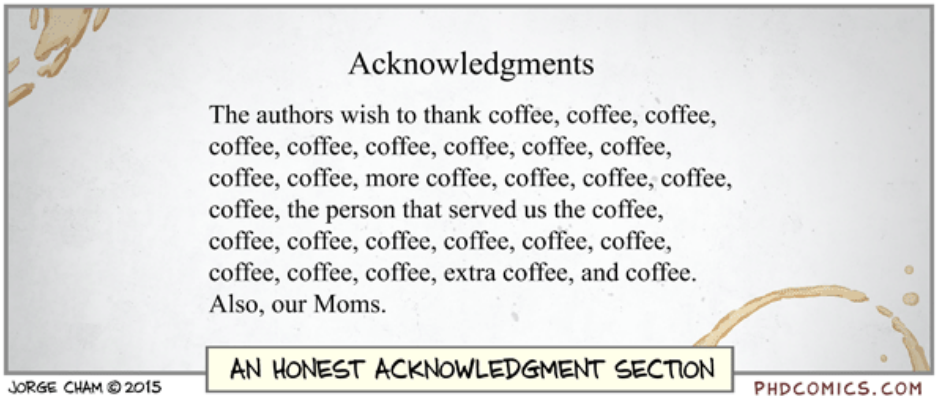
Почти 30% от човешкия епигеном се променя през първите 18 месеца от живота. Това предполага, че постнаталният прозорец на развитие предлага значителни възможности за установка на епигенетични и метаболитни адаптации към ранните хранителни условия. Съдържанието на холестерол в кърмата се приема е важно както за своевременното, така и за дългосрочното здраве на поколението. В Глава 3 изследвахме механизмите за регулация на съдържанието на холестерол в млякото, като разгледахме връзката между хиперхолестеролемия при майката и ефекта й върху нивата на холестерол в кърмата. Резултатите ни показват, че количеството холестерол в кърмата се поддържа постояно при различни степени на хиперхолестеролемия, посредством процеси, независими от холестероловите транспортни белтъци Abcg8 и Ldlr. Силната опозиция срещу промени в концентрацията на холестерол в кърмата предполага важна физиологична функция за този параметър. Епидемиологични наблюдения свързват кърменето с по-нисък риск от кардиометаболитни заболявания в напреднала възраст. Приета бе хипотезата, че количеството холестерол в кърмата има отношение към тези наблюдения и играе роля за предопредлянето на ключови параметри от метеболизма на холестерола при възрастните. Глава 5 описва експериментален модел на понижена наличност на холестерол от кърмата, при който бяха изследвани последствията върху стероловия метаболизъм във възрастни *Ldlr*–нокаут мишки. Посредством администриране на инхибитор на холестероловата абсобция, езетимиб, чрез млякото до новородените, бе намалена бионаличността на холестерол от кърмата през първите 3 седмици от живота. В

резултат на това, в 3 седмичното поколение се наблюдава понижена абсорбция, и редуцирани нива на тоталния и V(LDL)-асоцииран холестерол, подобно на ситуацията при бебета, хранени стандартна формула без холестерол. Въпреки че по времето на отбиване няма промени в генната експресия на чревия холестеролов транспортьор NPC1L1, в 24-седмични мишки пре-третирани с езетимиб, открихме значително понижена експресия както на гена, така и на белтъка, придружено от редуцирана абсорбция на холестерол в групата. Идентифицирахме повишени нива хистоновата модификация H3K9me3, знак за генно заглушаване, във близка до промотора на NPC1L1 зона, като вероятния механизъм обясняващ понижената експресия на NPC1L1. Заедно тези резултати демонстрират за първи път способността на червото при бозайници да изгради и поддържа активна метаболитна памет за хранителни условия от ранния живот, чрез предизвикани промени в епигенетичното регулиране на ключови гени. Разлики в нивата на кръвния холестерол или размера на атеросклеротични плаки формирани при двете групи животни не открихме. Въпреки, че моделът ни не обяснява ефектът на понижени нива на кръвен холестерол, който при хора се свързва с кърменето, резултатите ни предоставят ценни насоки за разработването на нови стратегии за трайно редуциране на плазмения холестерол в борбата срещу сърдечно-съдовите заболявания.

Също както западната диета, която съдържа високи мазнини и холестерол, диети, богати само на мазнини, предизвикват промени в червния микробиом, който е със значителен принос към негативното метаболитено въздействие на тези хранителни режими. Голямото количество хранителен холестерол води до увеличаване на проатерогенният серумен холестерол и асоциира със множество пато-физиологични промени. В Глава 4 изследвахме дали някои от тези промени не са индиректно предизвикани от въздействието, които хранителният холестерол може да окаже върху чревната микробиота. Резултатите ни показват, че при възрастни *Ldlr*-нокаут мишки, холестероловия компонент от диетата, сам по себе си не предизвиква големи промени в композицията на чревните бактерии, въпреки, че инициира значителни адаптивни изменения във цялостния стеролов метаболизъм на хоста. Това индикира, че силното въздействие на западните диети върху микробиотата е по-вероятно да се дължи на тяхното високо-мастно съжържание, отколкото на холестерола. Бъдещи изследвания биха показали дали холестерола като компонент от кърмата може да изграе роля при формирането на първичното чревно общество в ранните дни след раждането когато протича чревната колонизация.

В заключение, изследванията, описани в тази дисертация, предоставят

ценennи нови разбирания на комплексността от механизми въвлечени в програмирането на зрелия метаболизъм от фактори на ранната среда. Резултатите ни подчертават значимостта на феталния окислителен стрес и холестерола през ранното постнатално развиетие за за провокирането на дългосрочни промени в епигенетичния контекст на организма. Бъдещи изследвания ще бъдат насочени към откриването на епигенетично активни сензори за хранителни и други компоненти, които превеждат условията на ранната среда в изменена генна експресия, диктуваща адаптивния физиологичен отговор. Увеличаването на нашето разбиране за механизмите на метаболитно програмиране способства за разработването на нови стратегии за превенция или терапевтични интервенции в ранна възраст, които да подразположат основната популация към здравословно стареене и дълголетие.



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LIST OF PUBLICATIONS

1. Leberkuhne LJ, Ebtehaj S, **Dimova LG**, Dikkers A, Dullaart RP, Bakker SJ, Tietge UJ. The predictive value of the antioxidative function of HDL for cardiovascular disease and graft failure in renal transplant recipients. *Atherosclerosis* (2016) 249:181-185
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