Investigating mutational processes in intestinal stem cells in response to high fat diet

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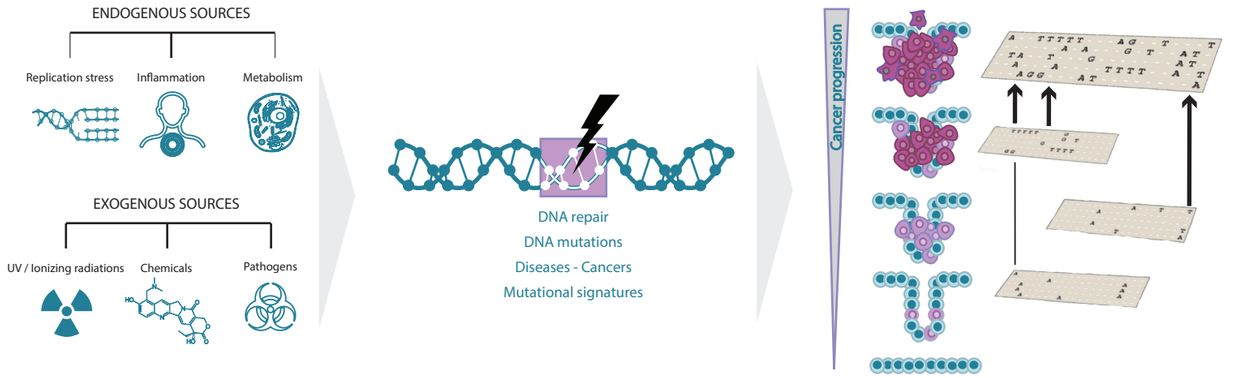
DNA damage | DNA repair | mutational signatures | intestinal stem cells

Abstract

Obesity has long been recognized as a modifiable risk factor of colorectal cancer (CRC) development. How diet induced obesity impacts genome stability in intestinal stem cells, the cell of origin of CRC, has not been systematically studied. Mutational signatures provide a new way of investigating the evolution of malignancies. However, many etiologies of known signatures remain unidentified, while endogenous factors involved in DNA damage and mutagenesis remain understudied.
This project aims to study how changes in the metabolism and inflammatory signaling due to diet induced obesity impact mutation generation and accumulation in intestinal stem cells. We established a bottom up and time resolved experimental system in vivo, in which we could track systemic and local changes in metabolism and inflammatory signaling and investigate the mutational outcome in clonally generated intestinal organoid cultures.

We observe trends toward accelerated aging in the HFD group, exemplified by an increase in signature 1 (canonical aging signature) and signature 18 (oxidative damage). We now seek to define the aging phenotype in terms of cellular and immunological markers, both on the systemic and local level. Finally, we aim to elucidate the connections between metabolomic and immunological changes and the increase in age specific mutagenesis observed in the intestinal stem cells of obese mice. This integrated knowledge will serve to open further avenues of investigation into cancer etiology and yield biomarkers for informative decision-making regarding lifestyle intervention methods for cancer prevention.

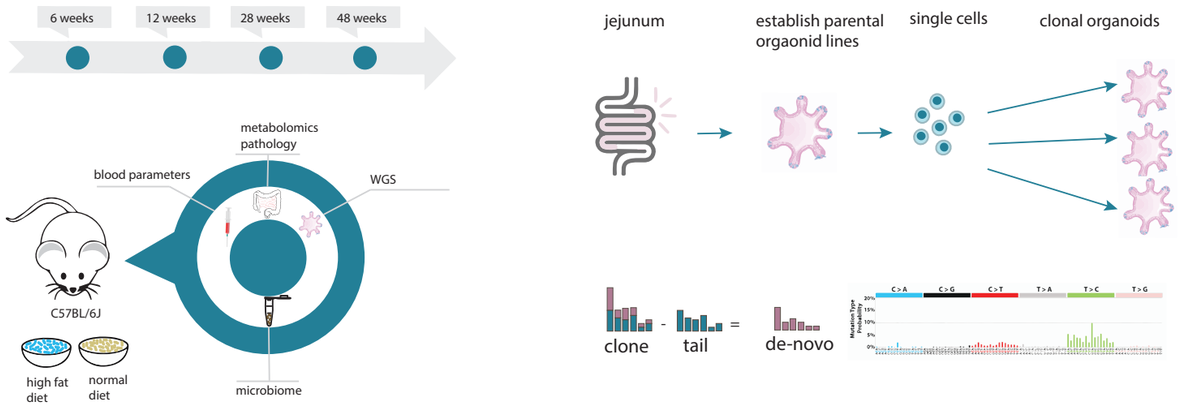
Mutational Signatures Record Consequences of DNA Damage and Repair Processes



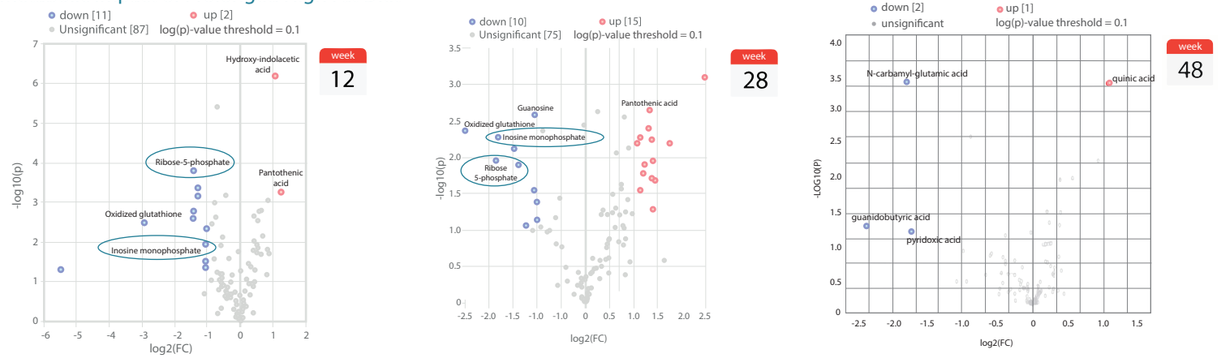
In 2013, Alexandrov et al. provided a new means to understand mutational processes in the evolution of cancer (1). By analysing whole genome sequencing data (WGS), they were able to extract distinct mutational signatures that contain patterns of base changes and clues to their mechanistic molecular origin. Since then, over 80 signatures could be identified and and a few linked to environmental factors as well as aberrant endogenous cellular processes.

While cancer sequencing data provided a first insight, they soon proved to be too noisy to elucidate clear causal relationships between an influence and a signature. Studies in isogenic cell models yielded a compendium of mutational signatures of environmental agents (2), to which, however, not every cancer patient has been exposed to. Endogenous factors and their interplay with DNA breakage and repair (3) are thus at the forefront of explaining how risk factors such as obesity, inflammation, and metabolism translate to molecular processes inside the cell that shape the evolution of a cancer.

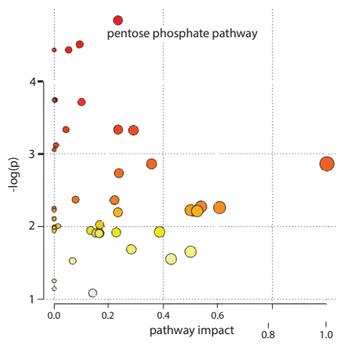
Studying the Emergence of Mutational Signatures Bottom Up



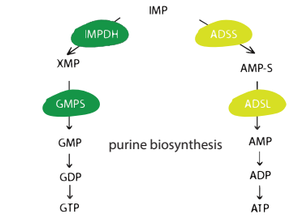
Metabolic Impact of Prolonged High Fat Diet

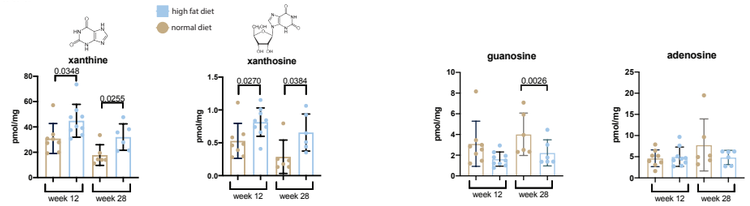


Metabolic profiles become increasingly dysregulated with age. Particularly purine nucleotide biosynthesis and metabolites of the upstream pentose phosphate pathway (PPP) are dysregulated with increasing age, leading to accumulation of metabolic intermeditates like xanthine and xanthosine, and possibly to imbalances in the nucleotide pool. The observed dysregulation of PPP and purine biosynthesis occur earlier in the HFD group than in the normal diet group, indicating an accelerated aging phenotype in the metabolic compartment.

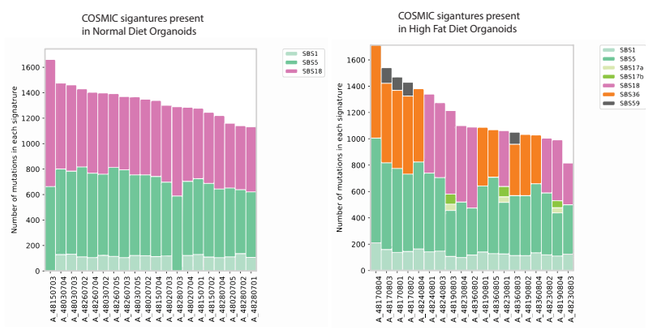


In the high fat diet mice, PPP and donwstream purine nucleotide biosynthesis is already dysregulated at the early time points (week 12 and week 28).
There is lowered ribose-5-phosphate in the HFD group (input for PPP), as well as a lower inosine-monophosphate(IMP) (output of PPP).
IMP is further utilized in purine biosynthesis, where an accumulation of intermediate products such as xanthosine might lead to misincorporation of these nucleosides into DNA and RNA.



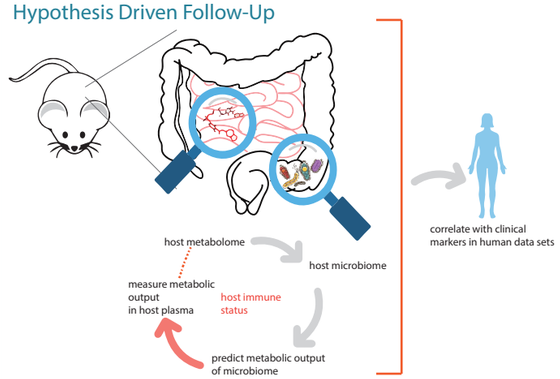


Mutational Signature Analysis Week 48



Non-negative matrix factorization (NMF) and subsequent decompoisiton into known and annotated COSMIC mutational sigantures identifies more signatures related to oxidative stress in HFD mice compared to normal diet mice. Strikingly, the canonical aging siganture SBS1is on avergage more active in the HFD mice, possibly indicating accelerating aging on the genomic level.

Hypothesis Driven Follow-Up



We hypothesize that an altered inflammatory environment drives the accelerated aging phenotype we observe. Our aim is to characterize known markers of aging and understand how they evolve under HFD conditions. While the analysis of other mutational features in the genomic data is ongoing, we are integrating our datasets to interrogate how the crosstalk between host metabolism and microbiome affects host immune status and other aging markers on the local (intestine) and systemic level.

References

1. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature. 2013;500(7463):415-421. doi:10.1038/nature12477

2. Kucab JE, Zou X, Morganella S, et al. A Compendium of Mutational Signatures of Environmental Agents. Cell. 2019. doi:10.1016/j.cell.2019.03.001

3. Zou X, Owusu M, Harris R, Jackson SP, Loizou JI, Nik-Zainal S. Validating the concept of mutational signatures with isogenic cell models. Nat Commun. 018;9(1):1744. doi:10.1038/s41467-018-04052-8

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