Diet and the epigenome

Yi Zhang & Tatiana G. Kutateladze

Over the past decade, remarkable breakthroughs in our understanding of epigenetic biology have coincided with an increased public interest in the impact of diet and lifestyle choices on health. It is well established that a balanced diet enhances life expectancy and helps to prevent or treat certain diseases, such as obesity, diabetes, cancer, and mental disorders. However, the biological mechanisms underlying these effects are not yet well understood. In this commentary, we highlight several recent studies that report on a potential link between dietary factors and alterations in epigenetic pathways, providing compelling insight into the possible effects of environmental factors on fundamental biological processes.

Two major elements of the human epigenome are covalent chemical modifications present on DNA and histones that define chromatin structure and are referred to as epigenetic marks. Epigenetic marks do not change DNA sequence, and therefore the entire genomic information or genotype, inherited from our parents remains untouched. However, epigenetic marks transform the local chromatin environment and thus affect DNA accessibility and regulate a wide range of DNA-templated processes, including gene transcription. Once misplaced or aberrantly active, epigenetic marks can disrupt normal gene expression profiles, incorrectly turning genes on and off. Dozens of epigenetic marks on histones and several on DNA have been identified, with methylation and acetylation of histones and methylation of DNA being the most prevalent. Unlike the fixed DNA sequence, epigenetic marks are less stable and can undergo changes during the cell cycle or in response to various stimuli required for normal cell growth and survival.

A wealth of recent studies suggests that epigenetic marks are also sensitive to environmental exposure. Nutrients, toxins, pollutants, pesticides and other environmental factors can impact, either directly or indirectly, levels and turnover of epigenetic marks. This in turn would result in transformed gene expression patterns and consequently affect our health for better or worse. Certain epigenetic alterations have been thought to pass to the next generation or cause a temporal modulation of subsets of genes eventually leading to progression of disease. Three studies recently published in Nature Communications have explored how diet or compounds found in food can alter gene expression programs through epigenetic mechanisms, opening a new avenue in exploring therapies based on these mechanisms.

How could food consumption influence epigenetic modifications that would eventually make an impact on individual health? One possibility is through directly affecting catalytic activities of the enzymes responsible for ‘writing’ or ‘erasing’ the epigenetic modifications. Wang et al. identified two phytochemicals—dihydrocaffeic acid (DHCA) and malvidin-3′-O-glucoside (Mal-gluc), metabolic intermediates derived from Concord grape juice, grape seed extract, and trans-resveratrol—that attenuate depression-like behaviors in mice. Using a mouse model, Wang et al. showed that treating mice with DHCA and Mal-gluc, which were added to drinking water, increased their resilience to stress and reduced depression-like behaviors. Specifically, the

---

1 Department of Pharmacology, University of Colorado School of Medicine, Aurora, CO 80045, USA. Correspondence and requests for materials should be addressed to T.G.K. (email: Tatiana.Kutateladze@ucdenver.edu)

DOI: 10.1038/s41467-018-05778-1
authors found that DHCA reduced expression of “methyl-DNA writer”—the DNA methyltransferase 1 (DNMT1). DNMT1 methylates intronic sequences of interleukin 6 (IL-6) genes, reducing level of this pro-inflammatory cytokine which has previously been implicated in the development of depressive disorders. Mal-gluc on the other hand reduced IL-6 level to baseline and simultaneously increased Rac1 expression, which contribute to the resilience against the development of depression-like phenotypes in mice. Overall, the study by Wang et al. provides striking evidence of how grape-derived metabolites affect host chromatin state, increasing histone polyacetylation and producing short-chain fatty acids (SCFAs). A “Western-type” diet rich in processed foods and high sugar drinks was found to limit microbial SCFAs production, prevent many of the microbiota-dependent events to occur, and lead to alterations in hepatic gene expression. Another example is the effect of a low-carb ketogenic diet that was shown to rescue hippocampal memory defects in a mouse model of Kabuki syndrome, characterized by loss of site-specific histone methylation and deficiency in chromatin opening. This diet promotes formation of β-hydroxybutyrate, an HDAC inhibitor, and leads to changes in H3ac and H3K4me3 in the hippocampus and rescue of the neurogenesis and memory phenotypes of these mice models.

It is inspiring to witness a gigantic leap in gaining knowledge of biological, mechanistic, and physiological aspects of epigenetics. Although much has been learned, we have only really scratched the surface in understanding the relationship between the fascinatingly complex human epigenome and environmental factors. The studies discussed above highlight potential roles of the environmental epigenetic changes that have to be put into the equation as we attempt to draw a comprehensive map of epigenetic networking. It will be exciting to see more studies dissecting the effect of dietary components on epigenetic imprinting, exploring alternative nutrition-based therapeutic approaches, and developing tools for personalized diet to improve health and increase life expectancy.

Received: 4 July 2018 Accepted: 26 July 2018
Published online: 28 August 2018

References
1. Huang, H., Lin, S., Garcia, B. A. & Zhao, Y. Quantitative proteome analysis of histone modifications. Chem. Rev. 115, 2376–2418 (2015).
2. Miska, E. A. & Ferguson-Smith, A. C. Transgenerational inheritance: models and mechanisms of non-DNA sequence-based inheritance. Science 354, 59–63 (2016).
3. Dawson, M. A. & Kouzarides, T. Cancer epigenetics: from mechanism to therapy. Cell 150, 12–27 (2012).
4. Shen, H. & Laird, P. W. Interplay between the cancer genome and epigenome. Cell 153, 38–55 (2013).
5. Zink, F. et al. Germ line-inherited H3K27m3 restricts enhancer function during maternal-to-zygotic transition. Science 357, 212–216 (2017).
6. Wang, J. et al. Epigenetic modulation of inflammation and synaptic plasticity promotes resilience against stress in mice. Nat. Commun. 9, 477 (2018).
7. Yuan, X. et al. Epigenetic modification of Fgf21 in the perinatal mouse liver ameliorates diet-induced obesity in adulthood. Nat. Commun. 9, 636 (2018).

It is inspiring to witness a gigantic leap in gaining knowledge of biological, mechanistic, and physiological aspects of epigenetics. Although much has been learned, we have only really scratched the surface in understanding the relationship between the fascinatingly complex human epigenome and environmental factors. The studies discussed above highlight potential roles of the environmental epigenetic changes that have to be put into the equation as we attempt to draw a comprehensive map of epigenetic networking. It will be exciting to see more studies dissecting the effect of dietary components on epigenetic imprinting, exploring alternative nutrition-based therapeutic approaches, and developing tools for personalized diet to improve health and increase life expectancy.

Received: 4 July 2018 Accepted: 26 July 2018
Published online: 28 August 2018

References
1. Huang, H., Lin, S., Garcia, B. A. & Zhao, Y. Quantitative proteome analysis of histone modifications. Chem. Rev. 115, 2376–2418 (2015).
2. Miska, E. A. & Ferguson-Smith, A. C. Transgenerational inheritance: models and mechanisms of non-DNA sequence-based inheritance. Science 354, 59–63 (2016).
3. Dawson, M. A. & Kouzarides, T. Cancer epigenetics: from mechanism to therapy. Cell 150, 12–27 (2012).
4. Shen, H. & Laird, P. W. Interplay between the cancer genome and epigenome. Cell 153, 38–55 (2013).
5. Zink, F. et al. Germ line-inherited H3K27m3 restricts enhancer function during maternal-to-zygotic transition. Science 357, 212–216 (2017).
6. Wang, J. et al. Epigenetic modulation of inflammation and synaptic plasticity promotes resilience against stress in mice. Nat. Commun. 9, 477 (2018).
7. Yuan, X. et al. Epigenetic modification of Fgf21 in the perinatal mouse liver ameliorates diet-induced obesity in adulthood. Nat. Commun. 9, 636 (2018).

It is inspiring to witness a gigantic leap in gaining knowledge of biological, mechanistic, and physiological aspects of epigenetics. Although much has been learned, we have only really scratched the surface in understanding the relationship between the fascinatingly complex human epigenome and environmental factors. The studies discussed above highlight potential roles of the environmental epigenetic changes that have to be put into the equation as we attempt to draw a comprehensive map of epigenetic networking. It will be exciting to see more studies dissecting the effect of dietary components on epigenetic imprinting, exploring alternative nutrition-based therapeutic approaches, and developing tools for personalized diet to improve health and increase life expectancy.

Received: 4 July 2018 Accepted: 26 July 2018
Published online: 28 August 2018

References
1. Huang, H., Lin, S., Garcia, B. A. & Zhao, Y. Quantitative proteome analysis of histone modifications. Chem. Rev. 115, 2376–2418 (2015).
2. Miska, E. A. & Ferguson-Smith, A. C. Transgenerational inheritance: models and mechanisms of non-DNA sequence-based inheritance. Science 354, 59–63 (2016).
3. Dawson, M. A. & Kouzarides, T. Cancer epigenetics: from mechanism to therapy. Cell 150, 12–27 (2012).
4. Shen, H. & Laird, P. W. Interplay between the cancer genome and epigenome. Cell 153, 38–55 (2013).
5. Zink, F. et al. Germ line-inherited H3K27m3 restricts enhancer function during maternal-to-zygotic transition. Science 357, 212–216 (2017).
6. Wang, J. et al. Epigenetic modulation of inflammation and synaptic plasticity promotes resilience against stress in mice. Nat. Commun. 9, 477 (2018).
7. Yuan, X. et al. Epigenetic modification of Fgf21 in the perinatal mouse liver ameliorates diet-induced obesity in adulthood. Nat. Commun. 9, 636 (2018).
Acknowledgements
Research in the Kutateladze laboratory is funded by the NIH.

Author contributions
Y.Z. and T.G.K. contributed to the writing of this manuscript.

Additional information
Competing interests: The authors declare no competing interests.

Reprints and permission information is available online at http://npg.nature.com/reprintsandpermissions/

Publisher's note: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2018