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Review

Honeybees and cell lines as models of DNA methylation and aging in response to diet

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ABSTRACT

DNA methylation patterns change as individuals grow older, and DNA methylation appears susceptible to modification by the diet. Thus DNA methylation may be a mechanism through which diet can affect aging and longevity. We propose that effects on DNA methylation also contribute to the extension in lifespan observed in response to dietary restriction. Relationships between diet-induced changes in DNA methylation and parallel effects on aging and/or lifespan could, of course, be purely associative. Proof of these ideas requires experimental model systems in which it is possible to manipulate genome methylation status and to measure effects on aging and/or lifespan. Commonly-used short-lived and genetically-malleable metazoan species, such as *Caenorhabditis elegans* and *Drosophila*, are not suitable for such studies; the *C. elegans* genome is not methylated, and DNA methylation in *Drosophila* is dissimilar from mammalian DNA methylation, occurring at cytosines at sites other than in CpG sequences. The honeybee provides a potentially unique and tractable model for such studies. Female larval development into the long-lived queen phenotype or short-lived worker is determined purely by diet (royal jelly) through an effect on DNA methylation, and honeybee DNA methylation mirrors that of the mammalian genome. Mammalian cell lines and biochemical approaches offer complementary tools to address specific components of hypotheses relating to effects of diet on aging through DNA methylation in a more targeted manner. Our studies using mammalian cell lines are revealing effects of Sirt1 on DNA methylation, and indicate that Sirt1 and resveratrol affect the expression of different sets of genes.

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1. Introduction

The pleiotropic effects of diet at all levels from systemic to molecular must be disentangled, yet their integrated effects understood, to harness most effectively the potential of diet to promote a long and healthier life. DNA methylation is affected by both diet and aging, and diet-induced DNA methylation effects may influence aging and lifespan. To study the effects of diet on aging and lifespan mediated through DNA methylation, we are developing a combined approach that exploits the tractability of cell line models but overcomes their limitations with respect to informing on systemic, in vivo effects through complementary research in the honeybee. This article provides an overview of some dietary interventions, including dietary restriction, that can affect aging and/or lifespan, explores the idea that DNA methylation may be a modifiable link between diet and aging/lifespan, explains why specific features of the honeybee make it a particularly good model for the study of diet-induced DNA methylation effects on lifespan, and highlights complementary cell-line-based approaches and some of our observations made using these tools.

2. Lifespan extension in response to dietary restriction

Diet can have a profound effect on lifespan and on physiological and metabolic features relevant to aging. Most notably, the practice of dietary restriction – reduced intake of macronutrients in the absence of severe nutritional deprivation – can extend lifespan. Observations demonstrating this response to nutrition have been made in species that cover an impressive breadth of phyla. For example, yeast grown in a medium providing a glucose at a lower concentration than is usual can continue cell division over a number of generations that is extended from the norm (i.e. an extended replicative lifespan) and also to divide more slowly (i.e. an increased chronological lifespan). Similarly, reducing the availability of the bacterial food source can extend lifespan in *Caenorhabditis elegans*, and *Drosophila* provided with a more dilute food source can live longer than flies on control diets (reviewed in Guarente and Picard, 2005). Similar responses have been observed in higher metazoa, including mammals; indeed the efficacy of dietary restriction to extend life was observed in rats as long ago as the 1930s (McCay et al., 1935). Evidence for effects of dietary restriction on longevity in humans is currently based largely on epidemiological observations, such as the unusually long lifespan of the population of the Japanese island of Okinawa where, culturally, it was usual to eat very sparingly

Abbreviations: DNMT, DNA methyltransferase; TOR, target of rapamycin; IGF1/insulin, insulin-like growth factor 1/insulin; AMPK, AMP-dependent protein kinase; SIRT, sirtuin; 10-HDA, 10-hydroxydecanoic acid; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha.

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(Willcox et al., 2006), and conclusive data are still lacking (Fontana and Klein, 2007). Positive responses to dietary restriction are, however, being observed in non-human primates. For example, reduced incidence of diabetes, cancer, cardiovascular disease and brain atrophy, and reduced mortality from age-related disease, were observed in rhesus monkeys under conditions of dietary restriction and, although not achieving statistical significance, more animals in the dietary restricted group survived to 30 years of age (Colman et al., 2009).

3. Other dietary interventions that may affect aging and/or lifespan

Specific dietary components with the potential to promote healthy aging and longevity, and particularly to mimic the response to dietary restriction, are the subject of vigorous research. Resveratrol, a polyphenol of particularly high abundance in the skin of red grapes, but also available in a range of other plant-derived foods, has received particular attention. Supplementation of the nutrient medium with resveratrol was shown to extend replicative lifespan in yeast (Howitz et al., 2003) and was also effective in extending lifespan in *Drosophila* and *C. elegans* (Wood et al., 2004). In mice, dietary resveratrol did not extend lifespan on a control diet but did increase survival on a high-fat diet and induced protective responses against obesity and insulin resistance, as well as inducing other metabolic and physiological effects associated with longer lifespan, including increased activity of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), increased mitochondrial number and improved motor function (Baur et al., 2006; Lagouge et al., 2006). The immunosuppressant drug rapamycin emerged recently as effective from an on-going large-scale screening program in mice for compounds with an ability to extend life (Harrison et al., 2009), establishing proof of principle for the efficacy of single agents to achieve such an outcome.

4. Mechanisms underlying aging and/or lifespan responses to diet

There are numerous mechanisms through which diet may affect aging and lifespan. Research into links between diet and aging or lifespan includes investigating modulation by diet or specific dietary factors of processes believed to play a major role in aging. Such processes include oxidative damage of cellular macromolecules, including phospholipids and DNA; cell senescence; autophagy; cellular accumulation of "debris" believed to contribute the aging cellular phenotype, such as glycated proteins; and mitochondrial biogenesis. Reference to these processes is to place in the broader context the idea that DNA methylation is another mechanism through which diet may modify aging, and further detail is beyond the scope of the current review. A number of recent review articles address some of these topics and include a dietary perspective (Hannigan and Gorski, 2009; Mandel et al., 2011; Martins et al., 2011; Valerio et al., 2011).

4.1. DNA methylation as a potential mechanism that mediates effects of diet on aging or lifespan

There is growing interest around the potential for diet-induced effects on DNA methylation to be a mediator of effects of diet on aging and/or lifespan. It is now well established that diet can influence epigenetic modification of the genome; effects of diet – and of specific dietary components – on DNA methylation in particular have now been observed in numerous studies. These studies have used a range of cell-line and rodent models, and also include observational studies based on human cohorts, and have investigated dietary factors including intermediates involved in 1-carbon (methyl) metabolism, bioactive polyphenols and isothiocyanates, zinc, selenium, arsenic, vitamin A and alcohol (reviewed in Mathers and Ford, 2009). DNA methylation patterns shift as individuals grow older, as reported in a growing body of literature emerging from studies in human cohorts examining both cross-sectional and longitudinal differences and measuring DNA methylation both globally and at specific sites (Bjornsson et al., 2008; Christensen et al., 2009; Issa et al., 1994; Kwabi-Addo et al., 2007; Rakyan et al., 2010; Teschendorff et al., 2010). An impact of environmental exposures, likely to include diet, on DNA methylation of the genome in humans was indicated in a landmark study uncovering differences in DNA methylation between monozygotic twins that were more marked in older pairs and in pairs who had spent more of life separated (Fraga et al., 2005). Our current research is pursuing the idea that dietary restriction may act – at least in part – through epigenetic effects, and in particular effects on DNA methylation (Ford et al., 2011; Wakeling et al., 2009). Earlier work by other groups indicated that dietary restriction can alter DNA methylation; under conditions of dietary restriction, mice exhibited global DNA hypomethylation in the liver and age-dependent changes in methylation of the *c-myc* oncogene were suppressed (Miyamura et al., 1993), and hypermethylation of the *c-Ha-ras* oncogene in pancreatic acinar cells was measured in rats (Hass et al., 1993). Data on human subjects indicative of effects of reduced energy intake on DNA methylation are now emerging. For example, three loci showed increased methylation in DNA from subcutaneous adipose tissue in overweight or obese postmenopausal women after a 6 month hypocaloric dietary regime (Bouchard et al., 2010), and methylation at two loci in DNA from peripheral blood mononuclear cells was increased in overweight or obese men after an 8-week hypocaloric weight loss diet (Milagro et al., 2011). Given that these differences in DNA methylation were induced under conditions of reduced energy intake in overweight or obese individuals, their relevance to effects on DNA methylation in response to dietary restriction as an intervention that can extend lifespan when undertaken by healthy individuals is open to question.

5. The need for tractable models for studies on diet-induced effects on DNA methylation and their potential consequences for aging

There is certainly a good reason to predict that age-related changes in DNA methylation could drive aging and age-related disease processes through deregulation of the expression of genes and pathways with specific roles in maintaining an optimally functioning cell and tissue phenotype, as well as through more global effects including genome destabilization (Eden et al., 2003; Gaudet et al., 2003) and loss of telomere integrity (Gonzalo et al., 2006). However, such links have not yet been demonstrated. Indeed, showing such causal relationships is a major challenge. Pharmacological tools to manipulate DNA methylation (such as genome-wide demethylation using the DNMT (DNA methyltransferase) inhibitors 5-azacytidine and 5-aza-2′-deoxycytidine) are crude, but nonetheless can be informative; restored expression of a silenced gene after administration of these compounds to rodents or treatment of cell lines is good evidence of an effect of DNA methylation on expression, providing that parallel measurements of DNA methylation confirm a reduction in response to the treatment at the relevant gene locus. Particularly informative experiments may include manipulation of the genome methylation status of experimental metazoan species and observation of effects on lifespan; transgenic mouse models with altered DNA methylation resulting from manipulated expression of DNMTs or other proteins involved in the maintenance of DNA methylation patterns may have utility here. While *Dnmt1* knockout is embryonic lethal (Li et al., 1992), mice with hypomorphic *Dnmt1* alleles, from which expression is reduced (but not abrogated) by targeted disruption of specific sites in the gene, have proved informative (e.g. Oghamian et al., 2011), and tissue-specific, conditional *Dnmt1* knockout can be achieved (e.g. Endres et al., 2001) and may be an approach to understanding effects of DNA methylation on specific processes. Transgenic mice with over-expression of Dnmt3a have also been generated (e.g. Samuel et al., 2007), and may

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