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The role of Sirt1 in restricted energy intake

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Dietary restriction (DR) increases lifespan in a range of evolutionarily-distinct species[1–4]. The polyphenol resveratrol may be a dietary mimetic of some effects of DR[5]. The pivotal role of the mammalian histone deacetylase (HDAC) Sirt1, and its homologue in other organisms, in mediating the effects of both DR and resveratrol on lifespan and ageing suggest that it may be the common conduit through which these dietary interventions influence ageing[6,7]. The novel hypothesis is proposed that effects of both DR and resveratrol relevant to lifespan extension include maintenance of DNA methylation patterns through Sirt1-mediated histone deacetylation. Changes in methylation status of the genome with aging are well-documented[8–10]. The effects of manipulating histone acetylation by Sirt1 overexpression and resveratrol treatment on methylation of the LINE-1 retrotransposon, a surrogate marker of global DNA methylation, were examined in human intestinal Caco-2 cells, using a published combined bisulfite restriction analysis (COBRA) assay[11].

Treatment of cells with the HDAC inhibitor trichostatin A (0.3 μM for 48 h) resulted in an 18% reduction in LINE-1 methylation (n 16–30; $P<0.001$; Figure), supporting limited published evidence that manipulation of histone acetylation status can affect DNA methylation[12]. Sirt1 expression was undetectable by RT–PCR in Caco-2 cells and was substantially increased 72 h after transfection with a Sirt1 expression construct. Neither Sirt1 overexpression nor resveratrol (10 μM for 48 h) alone affected DNA methylation in Caco-2 cells, but together increased LINE-1 methylation by 30% (n 17–30; $P<0.001$, Figure), in support of the hypothesis. Future studies should investigate changes in histone acetylation and locus-specific changes in DNA methylation in this model system and determine the effects of DR and resveratrol in rodents on DNA methylation profiles to identify candidate genomic targets.

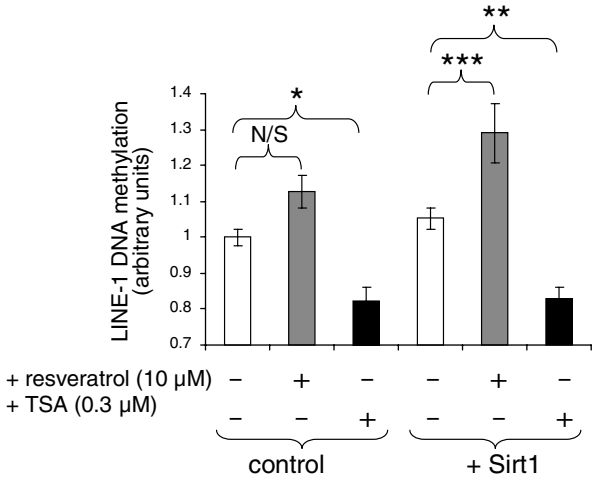

Figure. Effects of Sirt1 and resveratrol on LINE-1 methylation in Caco-2 cells. LINE-1 methylation was measured by densitometric analysis of SYBR green-stained COBRA gels. Data are normalised means with their standard errors (n 16–42). *$P<0.05$, **$P<0.01$, ***$P<0.001$ by one-way ANOVA then Bonferroni's multiple comparisons test.

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