Proceedings of the Nutrition Society (2013), **72 (OCE4)**, E192 doi:10.1017/S0029665113002176

Summer Meeting, 15–18 July 2013, Nutrition and healthy ageing

Epigenetic regulation of DNA base excision repair during ageing and dietary restriction

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Base excision repair (BER) is the primary mechanism used to fix oxidative damage to DNA. However BER efficiency declines with age[1,2]. To determine whether epigenetic events contribute to the ageing process through deregulation of BER gene expression we quantified DNA methylation and histone acetylation at BER-gene promoters (*Ogg1* and *Apex*) and BER repair activity in ageing and dietary restricted (DR) mice.

We measured promoter methylation by pyrosequencing in brain and livers from *ad libitum* (AL) and 40% DR mice at 3, 12, 24 and 30 months of age ($n = 5$–7/group). *Ogg1* promoter methylation decreased with age in the liver ($p = 0.018$) and brain ($p = 0.016$) and DR reduced *Ogg1* methylation ($p = 0.014$) in the brain. At 30 mo, we observed a 2.5 fold enrichment in histone 4 acetylation as measured by the ChIP assay in liver *Ogg1* promoter ($p = 0.004$) and a 2 fold enrichment at *Ogg1* ($p = 0.02$) and *Apex* promoters ($p = 0.031$) in the brain. *Ogg1* expression in the liver decreased by 40% with age and DR ($p = 0.0031$) and with DR only in the brain ($p = 0.002$). *Apex* expression did not change with age but was lower in DR animals ($p = 0.003$). A comet-based *in vitro* assay for BER incision activity[3] revealed no significant changes in either tissue. 8-oxoguanine lesions measured by HPLC-ECD decreased with age ($p < 0.001$) in the liver but not in the brain.

Table 1. Summary of results from the liver

	Methylation (%)		Acetylation (fold enrichment)		Expression (2^-ΔCt)		Repair (calculated from Tail Intensity)	Oxidative damage (8-oxodG/10E6dG)
Group	*Ogg1*	*Apex*	*Ogg1*	*Apex*	*Ogg1*	*Apex*		
3AL	1.76 ± 0.1	2.26 ± 0.6	0.86 ± 0.1	1.32 ± 0.4	0.0055 ± 0.0002	0.024 ± 0.002	15.2 ± 2.4	47.3 ± 2.6
30AL	1.19 ± 0.1	1.49 ± 0.2	0.73 ± 0.1	1.30 ± 0.3	0.0051 ± 0.0005	0.027 ± 0.004	15.7 ± 2.5	31.3 ± 1.5
30DR	1.11 ± 0.1	1.75 ± 0.3	2.59 ± 0.5	0.52 ± 0.1	0.0031 ± 0.0002	0.016 ± 0.001	15.0 ± 2.5	45.0 ± 1.6

Table 2. Summary of results from the brain

	Methylation (%)		Acetylation (fold enrichment)		Expression (2^-ΔCt)		Repair calculated from Tail Intensity)	Oxidative damage (8-oxodG/0E6dG)
Group	*Ogg1*	*Apex*	*Ogg1*	*Apex*	*Ogg1*	*Apex*		
3AL	1.28 ± 0.04	1.64 ± 0.1	0.50 ± 0.1	0.48 ± 0.1	0.016 ± 0.003	0.083 ± 0.010	3.0 ± 1.1	12.2 ± 0.4
30AL	1.07 ± 0.1	1.49 ± 0.3	1.27 ± 0.3	1.15 ± 0.3	0.012 ± 0.002	0.054 ± 0.006	2.7 ± 1.4	13.8 ± 2.8
30DR	0.81 ± 0.1	1.36 ± 0.1	0.41 ± 0.2	0.35 ± 0.2	0.014 ± 0.001	0.083 ± 0.008	4.9 ± 0.8	29.0 ± 12.8

In summary, our data suggest that epigenetic processes may contribute to transcriptional changes in BER-related genes during ageing and with DR.

This work was funded by the Research Councils through the Lifelong Health and Wellbeing Initiative.

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