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 $\underline{\text{Targeting Chromatin }}\underline{\text{Aging}}\text{ - The Epigenetic Impact of }\underline{\text{Longevity-Associated}}$   $\underline{\text{Interventions}}$ 

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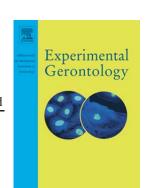
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CCEPTED MANUSCRIPT

"Targeting Chromatin Aging - The Epigenetic Impact of Longevity-Associated

Interventions"

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0.0 Abstract

A rapidly growing body of evidence has shown that chromatin undergoes radical alterations

as an organism ages, but how these changes relate to aging itself is an open question. It is likely that

these processes contribute to genomic instability and loss of transcriptional fidelity, which in turn

drives deleterious age-related phenotypes. Interventions associated with increased healthspan and

longevity such as reduced insulin / IGF signalling (IIS), inhibition of mTOR and energy depletion

resulting in SIRT1 / AMPK activation, all have beneficial effects which ameliorate multiple facets of

age-associated decline. The impact of these interventions on the epigenome is less certain. In this

review we highlight the potential of these interventions to act directly upon the epigenome and

promote a youthful chromatin landscape, maintaining genetic and transcriptional memory

throughout the lifecourse. We propose that this is a fundamental mechanism through which these

interventions are able to curtail the incidence of age-related disease. By revisiting these well

characterised interventions, we may be able to identify targetable effectors of chromatin function

and use this knowledge to enhance healthspan and longevity in human populations through the

measured application of dietary and small molecule interventions.

**Keywords** 

Epigenetics; Aging; Histone; Methylation; Longevity; Chromatin; Rapamycin; Insulin; Calorie

Restriction; Healthspan; mTOR; AMPK; SIRT1; IGF;

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