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Misexpression of Genes Lacking Cpg Islands is a Hallmark of Aging

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Abstract

Aging entails global disorganization of chromatin architecture characterized by disruption of the nuclear lamina and associated heterochromatin. How these structural changes contribute to age-related degenerative changes is unclear. We show that genes lacking CpG islands (CGI- genes), which form heterochromatin when transcriptionally silent, are globally misexpressed in aged nuclei with disrupted chromatin architectures. We demonstrate that CGI- gene misexpression is a common feature of mammalian aging and explains the molecular basis of various age-associated defects, ranging from loss of cellular identity and increased transcriptional noise to age-associated uncontrolled expression of secretory proteins, including signaling molecules putatively causing chronic inflammation. Our findings reveal that CGI- gene misexpression is directly associated with age-related physiological deterioration, thus provide a novel biomarker of aging.

Keywords: Aging, Chromatin architecture, Gene regulation, CpG islands, Heterochromatin, CGI- gene misexpression, aged tissues, mammalian promoter-associated elements, RNA-seq data, aged cells

Abbreviations: CGI- CpG island; DO- Diversity Outbred; LBR- Lamin B receptor; KD- Knock-down; SASP- senescence associated secretory phenotype

Introduction

Changes in the 3-D architecture of chromatin are observed in various diseases and are also a hallmark of aging. Disruption of the nuclear lamina and associated heterochromatin are commonly observed in various aging contexts, including premature aging diseases [1,2], cellular senescence [3,4], and normative aging [5]. Although these conserved structural changes have been reported for over two decades, their impacts on transcription and contribution to age-related degenerative changes remain unknown.

Our recent computational approaches demonstrated that CGIs, mammalian promoter-associated elements, provide important clues to answering this question. Specifically, we found that only genes not associated with CGIs (CGI- genes) reside within lamina-associated heterochromatin when they are transcriptionally silent. In contrast, genes associated with CGIs (CGI+ genes) remain as euchromatin even when repressed [6–8]. Based on this evidence, we hypothesized that heterochromatin decondensation during aging would specifically result in the uncontrolled expression of CGI- genes. We tested this hypothesis through large-scale transcriptome and proteome analyses of DO mice, which are a genetically diverse mouse resource that mimics the complexity of the human population with variable rates of physiological aging [9,10], and validated our results both using mice with disrupted nuclear architectures and through systematic meta-analysis of published transcriptome profiling data in our most recent study [11].

Disorganization of nuclear architecture during aging drives CGI- gene misexpression

Our DO mouse transcriptome analysis indeed demonstrates that over 30% of CGI- genes are mis-activated in aged kidneys and hearts compared to young tissues, and this pattern coincides with disorganization of chromatin architecture. Our experimental validation using model mice with disrupted nuclear architectures, as well as meta-analysis of RNA-seq data generated from conditions mimicking aged nuclei further demonstrate that nuclear architecture disruption is sufficient to induce heterochromatin decondensation and CGI- gene misexpression as observed during aging Upper part of (Figure 1). Our data also show that nuclear architecture disruption and resulting CGI- gene misexpression are directly associated with physiological deterioration of aged organs.

Misexpressed CGI- genes is responsible for physiological deterioration during aging

Notably, CGI- gene misexpression explains the molecular basis of various degenerative changes previously reported throughout the aging process Lower part of (Figure 1). For example, nuclear architecture disruption leads to the expression of tissue-specific

CGI- genes in tissues where they are not normally expressed. Our single-cell RNA-seq analyses reveal that CGI- gene misexpression is responsible for age-associated transcriptional noise (cell-to-cell transcriptional variability). These data indicate that disrupted regulation of CGI- genes during aging results in loss of functional identity of aged cells. We also show that uncontrolled secretory phenotypes commonly observed during aging, such as SASP [12,13], are largely attributable to CGI- gene misexpression. Our findings indicate that nuclear architecture disruption and resulting CGI- gene misexpression drive disruption of intercellular communication and fuel chronic inflammation in aged tissues.

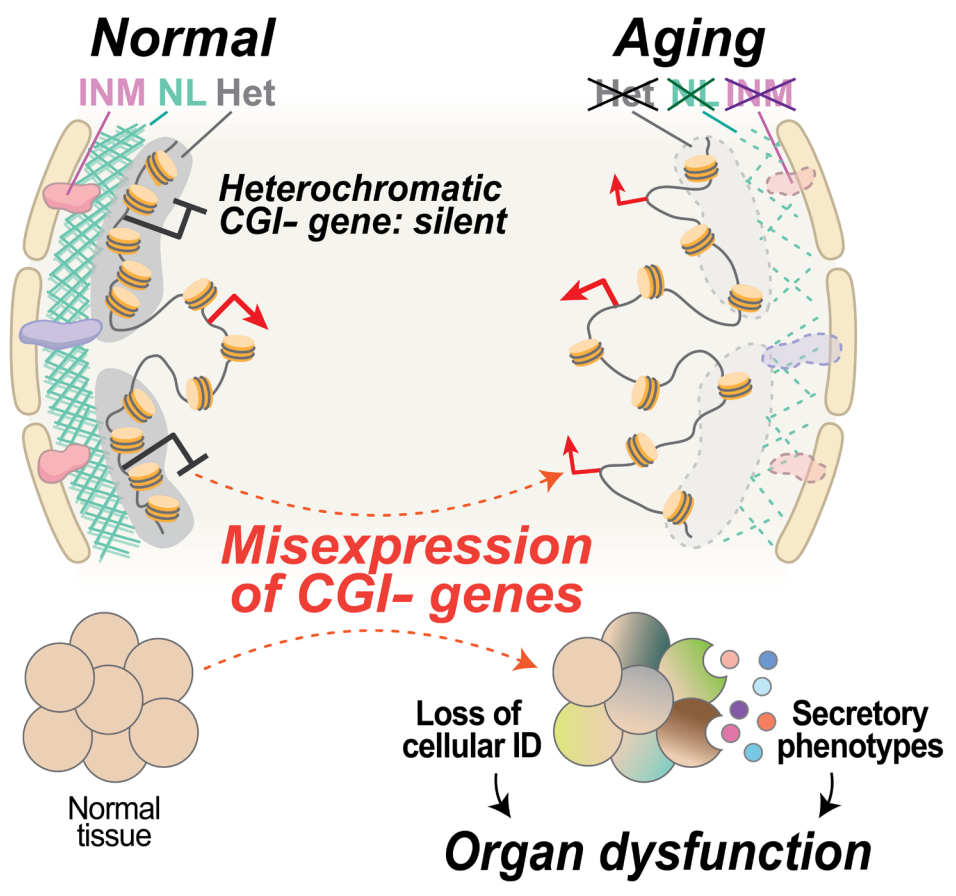

Figure 1. CGI− gene misexpression during aging. Aged nuclei exhibit loss of Nuclear Lamina (NL), Inner Nuclear Membrane (INM) proteins, and heterochromatin (Het). This disorganization of nuclear/chromatin architecture gives rise to uncontrolled expression of CGI− genes during aging, which causes age-related degenerative changes.

CGI- gene misexpression is a common feature of aging and age-associated diseases

Our large-scale meta-analysis of transcriptome profiling data further demonstrates that CGI- gene misexpression is a common feature of mammalian aging and age-associated diseases. Various aged tissue types, such as brain, liver, and muscle, significantly misexpress CGI- genes compared to young tissues. Interestingly, CGI- gene misexpression can be suppressed by previously validated anti-aging interventions, such as caloric restriction, rapamycin/acarbose treatment, and heterochronic parabiosis. Lastly, a broad range of age-associated diseases, such as myocardial, neuro-degenerative, hepatic, and macular diseases, also exhibit dramatic CGI- gene misexpression compared to healthy controls. These results demonstrate that CGI- gene misexpression provides a novel biomarker for physiological deterioration associated with aging.

Conclusion

Our study establishes that loss of transcriptional homeostasis of CGI- genes is a shared trait of mammalian aging, providing a fundamental basis for understanding aging and its associated degenerative changes. Our data also suggest that age-associated CGI- gene misexpression is a novel biomarker of physiological aging which offers an effective therapeutic target for delaying

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or ameliorating degenerative changes associated with aging/the aging process.

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Conflict of Interest

The authors declare that they have no competing interests.

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