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Effects of H3K9me3 on DNA Damage Susceptibility in Human Premature Aging diseases

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Background

- Premature aging diseases are rare genetic disorders that lead to accelerated cellular and organismal aging. Most of these disorders are consequence of defects in specific DNA repair genes. It can be a good experimental model to study molecular aspects of aging.
- In many forms of premature aging, as well as in natural aging, there is a decrease in chromatin density (heterochromatin loss), which results in increased DNA damage that result in the accumulation of chromatin poly ADP-ribosylation (PAR)[1,2].

Hutchinson-Gilford Progeria

Werner Syndrome

Cockayne Syndrome

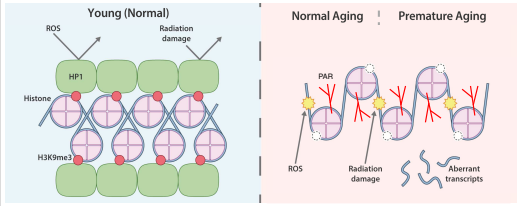

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Figure 1. Overivew of heterochromatin loss during aging. In young and healthy individuals, cells exhibit intact heterochromatin, a high level of H3K9me3, and a high level of HP1 bound to H3K9me3, which are factors that stabilize the heterochromatin complex. However, both chronologically and prematurely aged cells show decreased expression of core histones and reduced levels of H3K9me3, resulting in heterochromatin loss, DNA damage accumulation, accumulation of chromatin poly ADP-ribosylation (PAR) and the expression of aberrant transcripts.

Goal of the project

To find out if there is any alteration of heterochromatin content and DNA damage susceptibility in other types of premature aging disorders, Ataxia Telangiectasia[3] and Xeroderma Pigmentosum[4] that could be related to the molecular characteristics of the disease.

Results

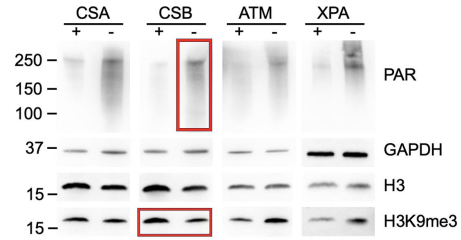

Figure 2. Heterochromatin alteration in premature aging diseases. Fibroblast cells were obtained from different types of premature aging diseases. (-), patient cells; (+), complimentary controls and probed for western blot using indicated antibodies.

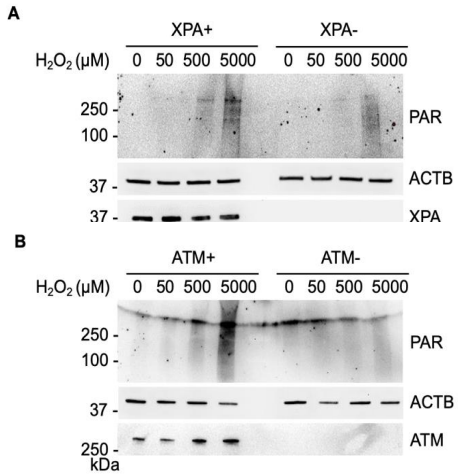

Figure 3. Altered DNA damage susceptibility to acute oxidative stress in XPA and ATM cells. Effects of H_2O_2 Treatment on PARylation in XPA and ATM cells. (A) PARylation increased in XPA (+) compared to XPA (-) cells when treated with 5000 μM of H2O2. (B) PARylation also increased in ATM (+) compared to ATM (-) cells when treated with 5000 μM of H_2O_2.

Conclusion

- Our results indicate that there may be a strong inverse correlation between DNA damage susceptibility and H3K9me3. Under oxidative stress induced conditions, mutated ATM and XPA cells, which have increased H3K9me3, had less DNA damage.
- Thus, this can confirm that alterations to chromatin structure that promote heterochromatinization is preferential in minimizing susceptibility to DNA damage.

Future Directions

We found inverse correlation between H2O2-induced DNA damage susceptibility and H3K9me3 in XPA and ATM cells (Figure 3). However, the higher basal PAR level in normal conditions indicates more steady-state DNA damages in CS, XP, and AT cells (Figure 2).

- Investigating the mechanisms underlying increased basal PAR despite of decreased damage susceptibility in AT and XP patient cells.
- Given the severity in consequences in most premature aging disorders is contributed by the persistence of non-functional DNA repair proteins, if additional studies were to confirm the significance of H3K9me3 in reducing DNA damage susceptibility, this would have tremendous implications on identifying the most effective treatment options for premature aging syndromes.

References

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