

Report 18: Acquired DNA modification (both DNA sequence and epigenetic modifications) may provide an integrated dosimeter of environmental exposure and be a useful predictor of disease

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Brief History: A central problem of environmental health science is that exposures often take place years prior to disease and do not persist in the body. DNA is one of the few molecules capable of capturing this information and this record can persist across many years and cell divisions. In addition these DNA modifications may be directly important in the etiology of disease. Rapid advances in DNA sequencing and related technologies make it possible to characterize such changes in single cells or small populations of cells. Although other Institutes are characterizing inherited variation in the genome and epigenome and modifications with disease state, they are not characterizing the induced changes that come from exposure. NIEHS can lead this effort

Discussion Highlights:

- Technologies for characterizing vast amount of genetic and epigenetic modifications are just now available opening a tremendous opportunity.
- Although it is assumed that mutations/modifications accumulate with age and exposure, this has not been directly documented.
- A number of important low hanging fruit exist that NIEHS can quickly harvest and become a leader in the field:

What is the rate of accumulated modification in somatic stem cells?

Do modifications increase with age (e.g. by comparing rate in young vs. old)?

Are rates of modification tissue specific?

Do environmental exposures affect rate of modification (e.g. comparing sun exposed vs. sun unexposed skin; dioxin exposed people vs. unexposed)?

Are modification rates affected by inherited genotype (e.g. SNPs in DNA repair, metabolism).

Does diet affect rate of accumulated modification?

-By investigating both sequence and epigenetic modifications (methylation, histone modification, miRNAs) we can investigate exposures that are both genotoxic and those that are not genotoxic.

Recommendations:

NIEHS should be leader in the field of acquired genetic/epigenetic somatic (stem cell) modification from exposure, diet, and aging

Patterns of modifications can be linked to environmental disease which can in turn be used to identify exposures that cause disease

RFA to gather best ideas for technologies and approach for using DNA as dosimeter

Opportunity to use both selected model systems/cell lines, animal, human populations

Environmental ENCODE project to select systems/exposures for detailed annotation

Discussion Participants: Begley, Bernstein, Hanawalt, Kemp, Shaughnessy, Williams, Zeldin, Pollock, Seewaldt, Adelman, Fargo, Others?