Developing a Mitochondrial DNA Diagnostic Platform for Skin Cancers

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Abstract
Non-melanoma skin cancer is the most common form of cancer diagnosed in Ireland1. It is most commonly caused by exposure to UV light, which promotes carcinogenesis through mutations in DNA2. There are many copies of mitochondrial DNA (mtDNA) in every cell, and this mtDNA population can be heterogeneous, with wild type copies present alongside mutations, which persist and indeed accumulate throughout an individual’s life3. Qualitative PCR enables the comparison of the frequency of mutated DNA compared to wild type in an individual’s sun-exposed skin using their unexposed skin as a baseline control. Results indicate that specific mtDNA damage occurs due to cumulative sun exposure, allowing the conclusion that mitochondrial DNA has potential to serve as a diagnostic platform for future skin carcinogenesis.

Introduction
Mitochondria are discreet organelles within cells, having a 16569 base pair genome distinct from nuclear DNA. MtDNA carries the code for 37 genes, 13 of which are templates for essential polypeptide subunits of the electron transport chain, responsible for production of ATP4 and located within mitochondria. Most cells have many mitochondria, each with numerous copies of mtDNA.

UV light has been called a complete carcinogen with no safe dose5,6, due to its ability to damage DNA. MtDNA has no protective histone proteins and limited repair mechanisms, but because of the high copy number of mtDNA genomes in skin cells, damage can persist whilst the cell remains viable and functions normally. A study to identify and characterise novel mtDNA damage markers such as large scale deletions that may act as predictors of skin damage can persist whilst the cell remains viable and functions normally.

A study to identify and characterise novel mtDNA damage markers such as large scale deletions that may act as predictors of skin cancer risk is underway and some early findings are presented here.

Methodology
Total DNA was isolated from human skin biopsies taken from sun-exposed and non-exposed sites. Specific mtDNA deletions and mutations were evaluated using conventional and Real Time PCR. Long-range PCR was also employed as a method of measuring global mitochondrial genome damage and identifying further non specific deletions.

Results
Specific mtDNA damage appears to occur due to cumulative sun exposure, and varies between individuals. Sun exposed skin shows greater levels of global mtDNA damage than unexposed skin in the same individual.

Conclusions
Specific mtDNA damage events appear to accumulate with cumulative sunlight exposure. Non-specific mtDNA damage identified by long-range PCR invites further investigation to characterise novel DNA deletions and mutations.

Future work will evaluate whether and to what extent damage events can also be linked to cancerous skin such that a mitochondrial diagnostics platform for skin cancer biomarkers can be developed.

References
1) Irish Cancer Society, Causes and prevention of skin cancer, 2013

Research funded by the Irish Research Council Embark Initiative (IRC RS/2012/295)