Title
Emergence and Evolution of Mutational Hotspots in Sun-Damaged Skin

Journal
Journal of Investigative Dermatology, 138(1)

ISSN
0022-202X

Authors
Cheng, Jeffrey B
Cho, Raymond J

Publication Date
2018

DOI
10.1016/j.jid.2017.09.007

Peer reviewed

HHS Public Access

Author manuscript

J Invest Dermatol. Author manuscript; available in PMC 2019 January 01.

Published in final edited form as:

J Invest Dermatol. 2018 January ; 138(1): 16–17. doi:10.1016/j.jid.2017.09.007.

Emergence and evolution of mutational hotspots in sun-damaged skin

Jeffrey B Cheng[1] and **Raymond J Cho**[2]

[1]Department of Dermatology, UCSF and Veterans Affairs Medical Center, San Francisco, California, USA

[2]Department of Dermatology, University of California, San Francisco, California, USA

Abstract

In this issue, Albibas *et al* investigate the mutational nature of p53 immunopositive patches (PIPs) (Albibas 2017), ostensibly clonal proliferations commonly observed in sun-damaged skin (Jonason et al 1996). PIPs have long been suspected as lineal precursors to actinic keratoses (AKs) and cutaneous squamous cell carcinoma (cSCC). But what mutations actually give rise to PIPs, and how these relate to skin cancers, has never been experimentally defined. The considerable clinical and economic costs of monitoring and treating sun damaged skin demand we better understand the evolution of these common premalignancies.

Main text

This study, “Subclonal Evolution of Cancer-Related Gene Mutations in p53 Immunopositive Patches in Human Skin”, builds on Doug Brash’s seminal description of PIPs in 1994, which hypothesized that such populations result from a subset of *TP53* mutations that stabilize the protein. A harbinger of our modern understanding of human cancer(Jonason et al 1996), these findings suggested for the first time that human cells readily acquire mutations *in vivo* and even undergo clonal expansion without easily converting to malignancy. The high frequency of PIPs raised questions about whether only subpopulations of cell types with specific epigenetic programming are susceptible to cancer progression, or whether sets of mutations must occur in specific sequence to promote malignancy.

In 2015, Peter Campbell’s group biopsied and sequenced populations of sun exposed yet normal appearing human eyelid skin, discovering high frequencies of numerous mutations previously observed in cutaneous squamous cell carcinomas, including *TP53*, *NOTCH1*, and *FAT1* (Martincorena et al 2015). Extending Brash’s work, this study established that *TP53* mutation is in no way unique in its ability to establish common, proliferating cell populations *without* producing a malignancy. These clones appeared to be widespread,

Corresponding Author: Raymond Cho, UCSF Department of Dermatology, 1701 Divisadero St., 4th floor, San Francisco, CA 94143, USA. Raymond.cho@ucsf.edu.

Conflict of Interest

The authors state no conflict of interest.

Pullquote: This data supports the striking notion that adding mutations in any of 13 diverse cSCC-related genes to p53 immunopositivity still fails to produce clinically appreciable dysplasia.

overlapping, and in chaotic competition with one other without creating clinically obvious actinic keratoses or squamous cell cancers.

This conundrum – one might call it “abundant mutations but rare cancers” – is now known to be a general feature of human tissues. Gastrointestinal adult human stem cells are estimated to accumulate 40 novel mutations per year (Blokzijl et al 2016) and leukemia-associated clonal gene mutations are pervasive in hematopoietic cells of healthy, elderly adults (Xie et al 2014; Young et al 2016). To truly understand why mutations are so common yet so often do not produce cancers, we must undertake the painstaking work of tracing populations of cells as they acquire additional mutations. What mutations can be co-acquired without the obvious enhanced proliferation of a premalignant lesion? Does acquisition of specific groups of mutations lead to enhanced growth of clonal proliferations? What is the long-term course and fate of cells containing multiple cancer-associated mutations that do not progress to carcinoma?

Albibas *et al* approached this problem through detailed analyses of p53 immunopositive patches (PIPs) of epidermis (Albibas et al 2017). It is estimated that 29–64% of PIPs contain detectable p53 mutation (Robinson et al 2010). Utilizing PIPs as case-control samples offered two key advantages. First, it enabled mutational analysis of subpopulations of cells possibly arising from a *TP53* mutation, without extensive single-cell sequencing or sequencing of many very small clones. Secondly, this approach allowed a glimpse of the evolutionary forces within PIP clones, an important question given the known, high frequency of these lesions and their potential for serving as precursors in AK/SCC development (Rebel et al 2005).

Through targeted sequencing, the authors showed that PIPs have enhanced frequencies of mutations in multiple skin cancer-related genes. Specifically, 13 of 18 profiled skin cancer-related genes showed non-silent mutations unique to PIPs, which were absent in adjacent p53 immunonegative skin. Most PIPs possessed mutations in at least 3 of the 18 genes. Of the highly mutated genes recently discovered in normal sun-damaged skin, three showed high mutational frequency in PIPs (*NOTCH1*, *NOTCH2*, and *TP53*), whereas only *FAT1* mutation was assessed but not reproduced in these data. This data supports the striking notion that adding mutations in any of 13 diverse cSCC-related genes to p53 immunopositivity still fails to produce clinically appreciable dysplasia.

While p53 mutation is detected in 60% of PIPs, consistent with previous findings, all *TP53* mutations were subclonal. These findings raise the surprising possibility that, in many cases, *TP53* mutations may not themselves initiate PIPs, but are secondary events that make these cells detectable through immunohistochemistry. This hypothesis is supported by the detection of an additional 3 cancer-associated mutated genes in PIPs that were not enriched in normal sun-damaged skin by Martincorena *et al* and the discovery of clonal PIP mutations in 4 non-p53 genes. For some of these genes, p53 stabilization may be required for them to confer a selective growth advantage. Perhaps a specific sequence of mutations must occur to support proliferating, dysplastic neoplasms, serving as a key bottleneck in those growths capable of forming skin cancers (Durinck et al 2011).

While unable to directly observe the transition of PIPs into AKs or SCCs, the authors compared the mutational profiles of PIPs against those of AKs and SCCs, and the process of AK/BD malignant transformation into SCCs. Actinic keratoses, Bowen's disease, and cSCCs possessed mutations in 16 of the 18 examined cancer-related genes. In accord with the view that a minority of PIPs progress into AKs and SCCs, all 13 PIP mutated cancer-associated genes were also mutated in AKs, BD, and cSCCs, with 8 identical mutations shared between the two groups. In fact, profiling AKs or BD adjacent to SCCs revealed shared mutations in 16 cancer-related genes between matched contiguous samples, with instances of identical mutations in 11 of these genes. This is consistent with the view that some AKs and Bowen's disease beget SCCs.

These conclusions set the table for close examination of the junction between highly mutated but clinically normal lesions and early actinic keratoses. Mutations distinguishing these populations may not fully explain the genetic requirements of a squamous cell carcinoma, but expand our knowledge of how a keratinocytic lesion grows sufficiently to become clinically detectable. Given the vast burden of treating actinic keratoses in dermatology, finding means to subvert this transition would reduce a central burden of clinical practice.

Acknowledgments

JBC is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Number K08AR067243.

References

Albibas A, Rose-Zerilli M, Lai C, Pengelly R, Lockett G, Theaker J, et al. Subclonal Evolution of Cancer-Related Gene Mutations in p53 Immunopositive Patches in Human Skin. J Invest Dermatol. 2018; 138(1):189–198. [PubMed: 28844940]

Blokzijl F, de Ligt J, Jager M, Sasselli V, Roerink S, Sasaki N, et al. Tissue-specific mutation accumulation in human adult stem cells during life. Nature. 2016; 538:260–264. [PubMed: 27698416]

Durinck S, Ho C, Wang NJ, Liao W, Jakkula LR, Collisson EA, et al. Temporal dissection of tumorigenesis in primary cancers. Cancer Discov. 2011; 1:137–143. [PubMed: 21984974]

Jonason AS, Kunala S, Price GJ, Restifo RJ, Spinelli HM, Persing JA, et al. Frequent clones of p53-mutated keratinocytes in normal human skin. Proc Natl Acad Sci U S A. 1996; 93:14025–14029. [PubMed: 8943054]

Martincorena I, Roshan A, Gerstung M, Ellis P1, Van Loo P, McLaren S, et al. Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin. Science. 2015; 348:880–886. [PubMed: 25999502]

Rebel H, Kram N, Westerman A, Banus S, van Kranen HJ, de Gruijl FR. Relationship between UV-induced mutant p53 patches and skin tumours, analysed by mutation spectra and by induction kinetics in various DNA-repair-deficient mice. Carcinogenesis. 2005; 26:2123–2130. [PubMed: 16051635]

Robinson S, Dixon S, August S, Diffey B, Wakamatsu K, Ito S, et al. Protection against UVR involves MC1R-mediated non-pigmentary and pigmentary mechanisms in vivo. J Invest Dermatol. 2010; 130:1904–1913. [PubMed: 20237490]

Xie M, Lu C, Wang J, McLellan MD, Johnson KJ, Wendl MC, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nat Med. 2014; 20:1472–1478. [PubMed: 25326804]

Young AL, Challen GA, Birmann BM, Druley TE. Clonal haematopoiesis harbouring AML-associated mutations is ubiquitous in healthy adults. Nat Commun. 2016; 7:12484. [PubMed: 27546487]