A Systems Biology Approach to Host Analysis Predicts Susceptibility to HIV Acquisition

Danny Douek
National Institutes of Health

When considering what factors may predispose to or protect from HIV acquisition, a key question may be expressed thus: in a situation where all things are equal in terms of risk of exposure to HIV, why do some people become infected and others do not? We sought to address this using carefully case-controlled samples from HIV vaccine trials with the hypothesis that pre-existing phenotypic and genetic profiles are predictive of susceptibility or resistance to HIV infection. We measured plasma biomarkers associated with immune activation, innate and adaptive immune cellular surface phenotypes, gene expression profiles within innate and adaptive immune cells, gene polymorphisms found within the transcriptome dataset, and performed whole genome and targeted sequencing. We established accurate predictive models of HIV acquisition based on gene expression profiles and discovered novel host gene polymorphisms that confer protection from HIV infection.

Research Questions

1. Assuming all factors are equal in terms of risk of exposure to HIV, why do some people become infected and others not?
2. Does baseline inflammatory status protect or predispose to HIV acquisition?
3. Is HIV acquisition determined by our genes?

References

- Hammer SM, Sobieszczyk ME, Janes H, Karuna ST, Mulligan MJ, Grove D, Koblin BA, Buchbinder SP, Keefer MC, Tomaras GD, Frahm N, Hural J, Anude C, Graham BS, Enama ME, Adams E, DeJesus E, Novak RM, Frank I, Bentley C, Ramirez S, Fu R, Koup RA, Mascola JR, Nabel GJ, Montefiori DC, Kublin J, McElrath MJ, Corey L, Gilbert PB; HVTN 505 Study Team. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. N Engl J Med. 2013 Nov 28;369(22):2083-92. doi: 10.1056/NEJMoa1310566. Epub 2013 Oct 7. PMID: 24099601
- Passmore JA1, Jaspan HB, Masson L. Genital inflammation, immune activation and risk of sexual HIV acquisition. Curr Opin HIV AIDS. 2016 Mar;11(2):156-62. doi: 10.1097/COH.0000000000000232.

Environmental stress-Friend or foe. Adaptation and cytoprotive memory vs heat intolerance

Michal Horowitz
The Hebrew University of Jerusalem, Hadassah Medical Center

Of the physical factors, environmental temperature is ecologically the most important. In most environments it lacks spatial or temporal constancy. Evolution had produced a variety of strategies to exploit or deal with its hazards. Heat acclimation (heat adaptation under controlled laboratory conditions) recapitulates evolutionary adaptation to heat. It manifests an expanded dynamic thermoregulatory span, reflected in the intact organism by a lower temperature threshold for heat dissipation and delayed threshold for thermal injury. Collectively, thermal tolerance stems from enhancement of innate cytoprotective pathways, producing "ON CALL" molecules that can combat stressors to which the body has never been exposed via cross-tolerance mechanisms (heat acclimation-mediated cross-tolerance-HACT). The foundation of HACT lies in the sharing of generic stress signaling combined with tissue/organ- specific protective responses. HACT becomes apparent when acclimatory homeostasis is achieved, lasts for several weeks, and has a memory. HACT employs two major protective avenues: constitutive injury attenuation and abrupt post-insult release of help signals enhanced by heat acclimation. Using cardiac ischemia, brain hypoxia and brain hyperoxia models as a guide to understand the broader framework of phenotypic plasticity; we learn that HACT is enabled by a metabolic shift induced by constitutive enhancement of HSPs and HIF-1a. There is less injury caused by Ca^{+2} overload via channel or complex-protein remodeling, or decreased channel abundance. Epigenetic markers such as post-translational histone modification and altered levels of chromatin modifiers during acclimation, acclimation decline and re-acclimation suggest that dynamic epigenetic mechanisms controlling gene expression induce HACT and enable a rapid return of the protected phenotype, namely cytoprotective acclimatory memory. While heat acclimation is achieved upon exposure at the higher limits of the thermoneutral zone, sever heat stress may results in heat intolerance, which may last for several mo. Heat tolerance vs heat intolerance involves differences in the immune response, It has epigenetic signature and suggest a heat dose dependent recurrent response.

Research Questions

1) What are the upstream mechanisms and timing of within-life epigentic changes leading to heat acclimation?
2) How do these difer in the short term acclimatory phase?
3) What are the transcriptome-proteome interactions in the deaclimated phenotype?

References:

- Heat Acclimation-Mediated Cross-Tolerance: Origins in within-Life Epigenetics? Horowitz M. Front Physiol. 2017 28;8:548. doi: 10.3389/fphys.2017.00548.
- Epigenetics and cytoprotection with heat acclimation. Horowitz M. J Appl Physiol (1985). 2016 r 15;120(6):702-10..
- Heat acclimation memory: do the kinetics of the deacclimated transcriptome predispose to rapid reacclimation and cytoprotection? Tetievsky A, Assayag M, Ben-Hamo R, Efroni S, Cohen G, Abbas A, Horowitz M J Appl Physiol (1985). 2014 Dec 1;117(11):1262-77.