PLOS Science Wednesday: Hi Reddit, we're Michael Emerman and Lucie Etienne, and our PLOS Pathogens research looks at the role of host genes in preventing (or not) cross-species transmission of viruses

PLOSScienceWednesday [1] and r/Science AMAs[1]

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REDDIT

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Hi and thank you for doing this AMA! A couple of nitty-gritty questions about the research:

1. It seems like you have shown that Chimpanzee APOBEC3G is*sufficient* to protect against cross species SIV infection (Fig. 1B). But I don't see much in the way of evidence to support the idea that APOBEC3G is *required* to protect against cross species infection. Did you attempt any experiments to get at the requirement for APOBEC3G in this context? This seems especially important given the nature of the sufficiency experiments you performed (somewhat artificial: i.e. cancerous human T cell line, non-physiological overexpression of APOBEC3G etc..). Additionally, some papers in the literature have cast doubt on the key role of APOBEC3g in viral restriction (http://www.ncbi.nlm.nih.gov/pubmed/15613310, for example).
2. Suppose chimpanzee APOBEC3G is required for preventing cross species infection. How do you tease out the difference between chimpAPOBEC3G evolving to protect against chimpanzee infecting SIVs versus chimpAPOBEC3G evolving to protect against cross species infection? Is there a difference between these two ideas?

Thanks!

SirT6

Lucie: Great questions. 1. Indeed, we think that chimp APOBEC3G is sufficient to block monkey's SIV replication. And we did not only show this in the cell lines or over expression system but we also showed that on primary CD4 T cells from chimpanzees – which is a more relevant system.

About the idea that APOBEC3G is required to protect against cross-species transmission. We think that it is not one protein only that restricts cross-species transmissions, but rather numerous host proteins that serve as a barrier. However, in the case of chimpanzee APOBEC3G seem to be a major player.

Hello Michael and Lucie!

Do simians have a stronger defense against SIV's due to their cannabalistic practices and evolving defenses over time?

Also, in your opinion, what is the outlook of a *real* cure for HIV/AIDS? Its seems like I often hear about new research breakthroughs and successful trials in animals, yet I'm still waiting for the headlines blaring across every TV proclaiming that AIDS is curable/preventable in humans.

Playtz

Michael: We think that chimpanzees have a stronger defense because they have been exposed to these kind of viruses in the past. Its not really about cannabilism, but about the fact that chimps eat other monkeys that have SIVs.

There is a difference between cure and prevention. A vaccine against HIV is still not on the immediate horizon. Its a hard problem that many smart people are working on. Cure is even harder, progress is being made, but in small steps.

Hi Michael and Lucie! Thanks for taking the time out of your day to be on Reddit with us. My question to you both would be: If this APOBEC3G protein serves as an antiviral défense against SIVs, could we potentially chemically engineer similar proteins and use them to establish défense against HIV in humans? Cheers!

KinaseCascade

Michael: good question. Yes, I think we could engineer variants of proteins like APOBEC3G that would protect human cells against HIV. We are doing these kinds of experiments now. However, delivering these proteins to act against HIV in people is a much harder problem. Another approach is to look for small molecules that would change the structure of existing human innate immunity proteins so that they work better against HIV.

Lucie and Michael, thank you for this AMA. It is a fascinating topic.

I have four questions that I was hoping you could answer.

1. Could you explain your hypothesis in simple terms? I think you are indicating that chimpanzees have naturally evolved a protein that inhibits most SIV infections found in monkey species. Is this correct? And if it is, could you paint a richer picture than I just did?
2. Could we potentially synthesise similar proteins to inhibit human HIV infections in the future?
3. What led you to your hypothesis in the first place?
4. Any good field research stories?

thoughtpod

Michael: question 1: your summary is very good. That is it exactly. A richer picture is the concept that ancient viral infections has driven evolution of the innate immunity genes in ways that impact current resistance or susceptibility to modern viruses. We call this field "paleovirology." Here is a short review you can read about this approach: http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1000301

question 2: Yes, I think we could make variants of these proteins that could inhibit HIV in humans, but its not clear how we could use those proteins. Another approach would be to discover small molecules

that would alter the structure of the existing innate immunity proteins to protect against HIV.

Hey!

As a general question, at any point have you explored the topic of defective interfering particles (DIPs) and their possible effects in your experiments?

I was a co-author in a publication in PLOS Pathogens last year regarding the topic of DIPs in a mice and humans stimulating an antiviral response in certain scenarios. So just mildly curious!

GeoGuy909

Lucie: The lentiviruses we used have the same backbone (HIV with a gene reporter) in which we have taken out the original vif gene that we have replaced with Vif from SIVcpz (chimp's SIV = our positive control) or Vif from different monkey's SIV. And we always look at the infectivity of the viruses with monkey SIV Vif as compared to the positive control that bears the SIVcpz Vif. Because the system is the same, we can conclude that our differences in infectivity are only due to the differences in the origins of Vif, and we can exclude other factors.

I don't have a questions for you, I just want to say thank you for your work. I can only imagine that your lives are long hours, lots of coffee and a fair amount of stress. So thank you for what you do, we all appreciate it.

Frostsong

Michael: Thanks!

Could you make a cell membrane with the protiens that hiv attatches onto and fill the faux cell with lyposome structure to catch and destroy hiv?

flabitsmiten

Michael: There is a similar concept that people are working on which is giving people antibodies that will destroy HIV. This is better than making a cell membrane because the antibodies are more stable inside the body and would be easier to manufacture. This is a major focus of many groups right now. Its similar to the idea getting giving someone antibodies against rabies virus after a bite from an rabid animal.