Clinical Education Initiative
Support@ceitraining.org

HIV CONTROLLERS: IMPLICATIONS FOR HIV CURE/REMISSION

Bruce Walker, MD

6/23/2017

HIV Controllers: Implications for HIV Cure/Remission

[video transcript]

00:00:01

- [Jim] Welcome to Physicians' Research Network. I'm Jim Braun, the course director of the monthly meetings of PRN in New York City. Since our beginning in 1990, PRN has been committed to enhancing the skills of our members in the diagnosis, management, and prevention of HIV disease, as well as its co-infections and complications.

00:00:19

We hope this recording of Bruce Walker's presentation, HIV Controllers: Implications for HIV Cure and Remission will be helpful to you in your daily practice and invite you to join us in New York City for our live meetings in the future.

00:00:33

PRN is a not-for-profit organization dedicated to peer support and education for physicians, nurse practitioners, and physician assistants, and membership is open to all interested clinicians nationwide at our website prn.org.

00:00:46

And now allow me to introduce Bruce Walker, Director of the Ragon Institute of Massachusetts General Hospital, MIT and Harvard, Director of the Harvard University Center for AIDS Research, and Professor of Medicine at Harvard Medical School.

00:01:01

- [Bruce] I'm gonna talk about the immune system, the immune response to HIV, and the fact that the immune system generally does not succeed against this infection, but sometimes it does. And what we know about that and what the implications of that are for a cure. Everybody knows that if, you know, from the era when no treatment was available, that essentially natural immunity did not work.

00:01:31

The vast majority of people progressed to develop declining CD4 counts and clinical AIDS. So the question is why is the immune system so ineffective?

00:01:43

Well, we know that there are different ways that the body responds to viral infections. There are B cells that, that make antibodies, and there are two kinds of T cells- CD8 T cells and CD4 T cells. All of these have a receptor on the surface. B cells have something called the B cell receptor. Essentially, that's an antibody that's bound to the B cell that is made by that B cell. Something that's very analogous is the T cell receptor on T cells, and this is how the body's immune system basically engages and knows that, it engages with its environment. But let's talk about B cells in the first instance. What do B cells do?

00:02:30

Well B cells have this membrane-bound B cell receptor. If it comes in contact with virus and happens to be a B cell that recognizes that virus, then what happens is it's stimulated to become a plasma cell, and those plasma cells make lots of antibodies. And the goal of these antibodies would be to go and find those viruses and basically eliminate them. So the antibodies are basically the soluble form of the B cell receptor.

00:03:00

Why don't they work? Well, a major problem is rapid viral evolution. The virus as it replicates, because of the reverse transcriptase it makes mistakes, and it makes a lot of mistakes. So you get antibodies to the original virus that you're infected with, but the virus is constantly changing. And the antibodies that are made don't recognize that newly-evolving virus. As time goes on, you start to make antibodies to the evolving virus, but now the virus is even further ahead with its mutations. And so, the B cell response- these antibody responses- are always playing catch-up, trying to get to the point where they can sort of control all these different viruses. So that's one thing. Another problem is that on an intact virus, the envelope protein exists as a trimer- three copies that are sort of bound together. And what happens is that over a very short period of time, that those trimers fall apart. So you have an infected cell, or you have a virion. The trimers are falling apart, and they're exposing parts of the trimer that were never there in the beginning. They're only exposed once it falls apart. Now you get this immune response that's really going crazy after those exposed parts, but that does nothing to try and target the intact virus.

00:04:30

So that's the problem. You get all these antibodies to these previously unexposed parts, and so that actually almost serves like a decoy.

00:04:41

So another thing is that the envelope is heavily glycosylated. All this sort of bluish-purple stuff are glycans on the surface of the trimer. This is sort of the molecular vision of this that's become available recently. That bit of yellow in there is the CD4 binding site, but you can see that it's very hard for any antibody to get past those glycans. So that's another thing that's really a big problem.

00:05:08

And then another thing is that in order for these antibodies to actually work, they have to undergo extensive somatic hypermutation. Meaning that B cell response is generated, and then it has to undergo this mutational process to make the antibody binding site into a structure that can actually get through those glycans and touch the conserved part of the virus.

00:05:37

And I'll show you just a picture of this; which really takes years if the neutralization sites tend to be the part of the protein of the virus. And you've got to have this very long so-called CDR3 region to get down and recognize that and get past these glycans. So these affinity-matured antibodies take a very long

time to develop. And, in fact, antibodies that are very broadly neutralizing are generated only in a small fraction of people that are HIV infected.

00:06:11

Finally, there is rapid establishment of the viral reservoir. How quickly do you think the viral reservoir is established? It's actually from monkey models. It looks like within three days of being exposed to the virus you already have a latent viral reservoir where the virus is integrated into the host chromosome and you have lifelong infection. So there's very little time to act to prevent that from happening. And that gives a huge challenge for vaccine development. So that's sort of B cells, and that's why we have problems in terms of the B cell response in controlling HIV.

00:06:47

What about CD8 T cells? So CD8 T cells have a T cell receptor and they express CD8 on the surface. How do these things work?

00:06:56

Well a virus as it infects a cell, the cell really wants to tell the body that something bad is going on inside it. And it has this mechanism through HLA Class I, where the viral proteins that are being made are actually processed and presented at the cell surface on these HLA Class I molecules. That then, the presence of viral protein in the binding groove of an HLA Class I molecule is a signal to the immune response that something bad is going on inside that cell and the cell should be eliminated. That generates these so-called cytotoxic T cell responses, or killer cell responses. They're called Class I restricted, because they recognize peptide in the context of HLA Class I. And what they do is they bind through the T cell receptor and CD8. They bind that HLA peptide complex, and then they release these enzymes- granzymes and perforin- that essentially kill the virus-infected cell. Now ideally, that whole process happens before progeny virions are produced. And if you can kill the cell before those progeny virions are produced, you actually eliminate the infection, because the virus cannot survive unless it has its protective outer coating. And it only gets that as it buds from the surface of a cell. So if you have a really potent immune response, a CD8 T cell response, you can potentially eliminate a cell before it can go on to, and eliminate a virus-infected cell before it can release viruses to go on and infect another cell. So why are these things not effective? I just indicated that they at least in theory should be.

00:08:46

Well one problem is again this issue of rapid viral mutation. The virus is constantly changing, and if it mutates within those, those short protein segments that are being targeted by the CD8 T cells, that fragment of peptide, that's a virus that's bound to HLA Class I, then it no longer binds to Class I, and the CTL response is then ineffective. So immune escape is a big problem.

00:09:13

Immune exhaustion is another problem. People are probably familiar with checkpoint inhibitors as a new therapy for cancer. Checkpoint inhibitors were actually first discovered as playing a role in human diseases in the context of HIV-1 infection. And, in fact, what happens is that with chronic immune

stimulation PD-1 is upregulated on these killer cells. And it basically when it interacts with this ligand PD-L1, it shuts off the killer cell response prematurely. So essentially you have immune exhaustion occurring because PD-1 is getting expressed, and the cells are being turned off. And so those are really two of the main reasons why the killer cell response doesn't work.

00:10:07

What about CD4 T cells? These are cells that are actually the target of HIV infection, but they also are the central orchestrator of an effective immune response. In any kind of setting you have to have pathogen-specific CD4 cells to provide help to CD8 T cells and help to B cells.

00:10:31

Well what happens is that the cell has a second mechanism for alerting the body to the fact that it's infected. That's through HLA Class II expression. Different viral peptides are presented in the context of HLA Class II. These CD4 T cells come in and recognize that complex, and what happens is then they become activated and they produce these helper cytokines, which really gets the whole immune response going. Well it's pretty obvious, I think, what the problem is then for these things in HIV infection and why they're not effective, and that is because these very same cells once they become activated they express CCR5 and CD4- the co-receptors for viral infection. So these cells, you're trying to mount a good immune response. You're trying to get help to orchestrate B cells and T cells. And, in fact, those very cells that are getting activated are getting eliminated.

00:11:33

But the fact of the matter is some people actually control HIV infection. It was really at PRN that I first became aware of that from finding out from you all that you were following patients. We had found a patient who had an undetectable viral load in Boston that had, you know, never been treated. We were just amazed at that. And I thought, you know, we would probably never find another one of those, but it was here in talking with people that I asked the question; has anybody ever seen one of these? And, you know, over half the people in the room raised their hands. And that's when we realized these things actually do exist, and we started a study to try and understand what was going on. And the reason that these were so interesting to us is that there seems to be a transmission and progression threshold around 1,500 to 2,000 copies where the chance of progression and the chance of transmission is markedly diminished.

00:12:32

So we started this thing called the HIV Controllers Study. Many thanks to PRN providers for helping us with this. And the idea there was to try and find out what the heck was going on with these individuals. And we wanted to apply a sort of a non-biased approach to this: make no assumptions, but see if actually by doing some genetic studies, we could understand what was going on.

00:12:58

So what we did was something called a genome-wide association study. It was new at that time, and the idea was, the human genome basically has about three billion nucleotides, and there's no way you can

sequence all of those. But there are things called single nucleotide polymorphisms, and about a million of these single nucleotide polymorphisms essentially explain the variability in the HIV genome. And the idea behind this whole study was to try and find one of these polymorphisms that was one flavor in people that controlled and another flavor in people who didn't control, where it really segregated around one of those individual single nucleotide polymorphisms. An analogy is trying to understand why big dogs are big and small dogs are small. Well if you do a genome-wide association study, and you have a whole group of big dogs and a whole group of small dogs, you find something extraordinary when you do this. There's one SNP that's always one flavor in big dogs and another flavor in small dogs, and that's a SNP that is in the insulin-like growth factor gene, which is something that regulates cell size. So it makes perfect sense. Our idea was let's try and figure this out with HIV infection. So we got together, over 1,000 HIV controllers, and we compared them to progressors and we said, what's different, controller versus progressor? And we looked for whether we could find some place where we would see SNPs that were always one flavor and the opposite in the other group.

00:14:43

And so this is basically, there's a million data points on this slide. And there are so many in that one position in chromosome 6 that are significant, that it almost looks like a line there. So we found this incredible signal when we did this study. What is chromosome 6? Well chromosome 6 is actually the chromosome that encodes immune function, particularly the HLA Class I.

00:15:15

And so essentially what we saw as we went deeper into this was that these peptides I told you about that are on the surface of an infected cell, this is a representation of one of those. They tend to be eight to ten amino acids long. What we found was that it was amino acids lining this groove that were deterministic in terms of whether somebody was a controller or a progressor.

00:15:42

So essentially what we found was this strong association with the peptide binding groove of HLA Class I. So what do you think's going on? Is that what's controlling, or is that an indicator of in fact, cytotoxic T cells and their ability to recognize this complex. And that's actually what it ended up being.

00:16:04

So the major thing that controls, that makes a difference in terms of viral load and somebody's infected are CD8 T cells, the HIV-specific CD8 T cell response. And it's associated with specific HLA Class I alleles that present those peptides. So now let's ask the same question we asked before but a little bit differently. Why is it that controller CTLs work? Why are they so effective when they're not effective in other individuals? Well, remember the immune escape was one of the problems that I told people about.

00:16:46

Well it turns out that, for reasons that are still not entirely clear, controllers tend to target highly-conserved parts of the HIV virus, so that the virus can't really escape. If it does, it loses function. So

these are critical to the function of the virus. So it's actually hitting the vulnerable regions of the virus. The virus can try and mutate, but if it does it basically kills itself.

00:17:17

And the major area that these people target is the gag protein, which has this very complex structure with these hexagons and pentagons that form the capsid. And if you have mutations in that, then you can't really form the capsid so you can't really make a good infectious virus. The CD8 T cell response, these killer cells, are forcing the virus to mutate to become something it doesn't want to be and lessening its ability to cause disease.

00:17:52

Controllers also express specific HLA Class I alleles. Now why is that important? Well that binding groove kind of dictates- it's different on different HLAs- and it dictates what parts of the virus can actually bind. And there are certain HLA alleles that preferentially present conserved regions of the virus to the immune system. So that's another reason.

00:18:20

Another reason is this whole thing about immune exhaustion. For reasons that also are not entirely clear, PD-1 expression is not upregulated as much on killer cells from people that control spontaneously.

00:18:36

And the other thing is that controllers have preserved CD4 T cell help. Part of that is because they have other genetic factors that render their cells slightly less infectible. Because the cells are slightly less infectible, there's less downregulation of HLA Class I, which is mediated by Nef. They are able to provide more help to CD8 T cells. And again, since they're providing help and you've got these infected T cells, then the T cells are able to drive these mutations in the virus that make it less fit.

00:19:18

So why is it then, given all this, why is it that controllers don't eradicate HIV infection?

00:19:26

Well, we'll do a little bit more in the way of trying to explain some of the background immunology about HIV, and, in particular, I want to talk about lymph nodes now and what's happening in lymph nodes. And, in fact, it's in lymph nodes and in the gut lymphoid tissue that really, all of the action is happening in HIV infection. That's where the infection takes place. That's where the destruction occurs. And parenthetically, for years and years, we've tried to understand the immune responses in HIV infection by studying peripheral blood. But, in fact, as I'll come back to later, it's really the lymph nodes where we should be looking. It's just very difficult to do that because it requires somehow getting access to that lymphoid tissue, and that is not easy. But at any rate, this is what a lymph node looks like. You've got incoming lymph that then flows through the lymph node. These yellow structures are called follicles. They are areas that are rich in B cells. When a person becomes infected, dendritic cells capture virus and

take it to a draining lymph node. And the lymph nodes are basically where the immune responses are generated. So that's a key element in getting an immune response going.

00:20:54

So these dendritic cells end up coming in. They go to the B cell follicles. And in the B cell follicles, the presence of viral antigen causes a germinal center reaction. This is basically where the B cells and CD4 cells congregate together and affinity maturation occurs by these rounds of teaching the antibody to become more effective. Within that germinal center again you have T follicular helper cells and B cells. What you don't have in these follicles is killer cells, these CD8 T cells, because they're not, they don't have the right receptors to be able to get into those germinal centers. You have this situation going on. You have these activated T follicular helper cells. They're CD4 cells. If they're activated and they're CD4 cells, what's gonna happen to them? They're gonna get infected. So now you have in this germinal center, the body trying to make an effective immune response but it's, it's being refrained from doing that because the T follicular helper cells are getting infected by HIV. Now, again, just to point out. CD8 T cells are not able to get into that area. Well what about as these B cells are making antibodies, why don't the antibodies just clear that up? Well remember that early slide I showed you. The virus is always a step ahead of the immune response. So the virus is mutating even within these germinal centers, and so even as you're getting antibodies and they're affinity maturing and they're trying to do their job, the virus is always one step ahead and is not neutralizable by the antibodies as they're being generated.

00:22:52

And what is it that is required for something to get into a cell? Well, it's something called CXCR5. It's another receptor on cells. CD4 cells are able to express that, and that's how the CD4 cells, the T follicular helper cells, get into the germinal center. CD8 T cells generally don't express that. So if I take a person with chronic disease and I measure their CD8 T cells, their HIV-specific T cells, and look for CXCR5, I don't find it at all. And so those cells aren't getting in.

00:23:35

But look at what was first revealed by studying monkeys and has now been confirmed in humans. On the left is an elite controller monkey. The only place you can find virus in that monkey is in the germinal center. On the right is a progressor. Virus is all over the place. But there's this sanctuary in the elite controller where virus is still replicating within the follicle. We've been doing studies in South Africa where we've been getting excisional lymph node biopsies.

00:24:08

Here's a biopsy. In green is a stain for this germinal center and in red are CD8 T cells. I'm not showing it to you right here, but where the virus is in this individual is within this green area. Within the germinal center. You don't see CD8 T cells in that area. And if we look on the right by tetramer staining for CXCR5 expression, what you find is that on the HIV-specific CD8 T cells, there's really no CXCR5.

00:24:43

Contrast that now to what we see in an elite controller here in South Africa. And what you see now is throughout the lymph node, you see these red cells. So cells are actually getting in, and when you do the staining here, you see that their CD8 T cells actually express CXCR5. So it's not that they can't do it, but most people don't do that. But this immediately suggests something in terms of thinking about cure. What if you could engineer people's cells to express CXCR5, their killer cells? Could you then get them to go into these germinal centers and actually kill those residual virus-infected cells?

00:25:25

We've done studies in South Africa. Again, looking at multiple people from excisional lymph node biopsies. The greater the CXCR5 expression on these cells, the lower the viral load. So there's clear evidence that these things, when they're around, they are associated with a lower viral load.

00:25:50

And so what we see essentially to sum this up is that CXCR5 is expressed on CD8 T cells from elite controllers. And, in fact, those cells get into the lymph nodes. We've gone from, you know, I mean to me, it's been kind of an amazing journey that we've all been on. I was an intern when the first patients with HIV were reported in MMWR in 1981. And this disease was a total black box, and it seemed as time went on in those early years, like HIV was following completely different rules. But as it's revealed its secrets, it's just been amazing to see how it really does follow all the biological rules. And we've been learning its secrets and getting ideas about how we can basically counteract the clever ways in which it's been able to circumvent immune function. So definitely some people control HIV infection.

00:27:03

Are there adverse consequences of durable control of HIV? Well, yes there are, and I think this is a really important point.

00:27:12

One is that even among elite controllers, if you look at them in terms of their lymph nodes there's more lymph node fibrosis in people who are elite controllers. So even though you may not see that in the periphery, you see that in the lymph nodes. And often that's associated with the declining CD4 T cell number.

00:27:33

There's increased atherosclerosis related to immune activation. Now not all elite controllers are the same. It's a very heterogeneous group. Some have very high levels of immune activation. Some have very low levels of immune activation. Some have a gradual decline in CD4 numbers. Some have no decline in CD4 numbers. I would say that the bulk of the evidence suggests that if you have a stable high CD4 count and not much in the way of immune activation or high levels of CD8 T cells, that you actually are, are likely to do well without therapy.

00:28:17

If you treat people who are elite controllers, there is an impact on viral load when you look at single-copy assays, as studies done here from UCSF showed.

00:28:28

And there's also an impact on integrated DNA. So you can treat people and actually lower the level of cell-associated DNA.

00:28:44

And there's also a mild impact on immune activation when you look overall at individuals. Those that have high levels of immune activation can be brought down.

00:29:00

So there are a number of arguments for treating elite controllers. One is to decrease inflammation and the consequences of that. Another is to increase CD4 counts if people are having declining of counts. Another is to decrease replication competent HIV in reservoirs. There may be a decrease in atherosclerosis. There may be some decrease in lymph node fibrosis, and there may be some improvement in survival. But again, it's a heterogeneous group. Based on what we know, I think that it's important to share this with patients who may not want to go on therapy, but to have them understand that there are potential consequences. And also important for us to then monitor people in terms of advising, you know, in terms of how hard we push to get them on therapy.

00:29:57

Well, let me just end by giving a couple of implications from controllers for cure strategies. And this is really the area that I'm very excited about in terms of potential for going from somebody who spontaneously controls, to actually potentially achieving a cure. So it turns out that a small percentage of elite controllers make very potent broadly neutralizing antibodies. Do those antibodies work in the elite controllers? No, because their own virus has already escaped it. But if you take that antibody from an elite controller that's broadly neutralizing, it may neutralize 99 out of 100 viruses out there. The one that it won't neutralize is the person's own virus. But it'll neutralize all those others. Well, hey now you're talking. If you could clone that antibody and give it to the other 99 people, it might actually be effective. And, in fact, that's what's being done.

00:31:00

So there are a bunch of different targets for antibodies. This gray glob here in the center is actually the envelope trimer, and it just shows that these things bind at different areas. One of the areas that they bind is the CD4 binding site. And, in fact, 3BNC117 is one of those antibodies. It was derived from a New York patient who was referred by one of the providers here, and the antibody was cloned. It's been made as a clinical-grade antibody, and has been given to monkeys and to people.

00:31:33

And when you look at these antibodies, they dramatically suppress virus in either a monkey model or in humans as shown here.

00:31:42

The 3BNC117 has been in phase one studies. It's now being combined with a second antibody through people at the Rockefeller- Marina Caskey, Michel Nussenzweig- and is having a very potent effect in terms of lowering viremia in untreated individuals.

00:32:04

There are no data yet to indicate whether, nor have the studies been done appropriately to see if it could actually affect a cure.

00:32:10

But these are just data showing that you can get quite a good decline in viremia. What to me is really exciting is a study that was just published using these broadly neutralizing antibodies in combination in a monkey model. And so what happened here was that they took monkeys, they infected them, and then they started them on the broadly neutralizing antibodies. And what they saw was that these monkeys actually, even as the antibody wore off, some of them had some blip in viremia as seen here, but then they controlled spontaneously. No more antibody, no more treatment. They became essentially elite controllers. So a substantial fraction of those monkeys became elite controllers by just getting broadly neutralizing antibodies. So what the heck is going on?

00:33:07

Well, what we think is going on is that when you have the broadly neutralizing antibody and you release a virus so that it starts to replicate, the broadly neutralizing antibodies effectively bind to the virus. That creates an immune complex which is highly immunogenic. So that actually then drives an HIV-specific immune response. That immune response we think may be incredibly effective because it's being generated in the presence of effective CD4 T cell help, because the CD4 cells are not getting infected. Because the antibody's protecting them. So you've got virus around. It's not infectious. It's getting complex with antibodies, taken up by an antigen-presenting cells, generating this terrific immune response. And, in fact, what we would anticipate is that it would generate strong CD8 T cell responses, which are the things that control in elite controllers.

00:34:08

So when you take those same monkeys that had been initially treated like this one. They were initially treated with antibody for a brief period of time. The antibody wore away. Virus is completely controlled. Now you deplete CD8 T cells, the thing that we think is controlling. If you deplete those, what happens to viral load? It comes roaring back. Very clear evidence that the CD8 T cells are actually doing this. And that was true in every one of these animals, that when you get rid of the CD8 T cells, virus comes back. So the immune system is controlling in these monkeys, and the question is, can we get to the point where we can do that in humans. On top of that, can we use these broadly neutralizing antibodies to

actually get them into the germinal centers, where the sanctuary is for virus that in those T follicular helper cells. Not dendritic cells, but T follicular helper cells that are in the germinal centers. If the antibody, an effective antibody can get in there, we may be able to eliminate that virus.

00:35:17

So the conclusions here are that, HIV-specific killer cells, CTL, CD8 T cells are all the same thing. They're the main effector response controlling HIV in elite controllers. Elite control is partially mediated by forcing the virus to be something it can't; it doesn't want to be, so it becomes less fit. Broadly neutralizing antibodies develop only in a minority of people who are elite controllers. And exactly why only some of them generate these is not so clear and something that we would love to understand more about. But they do develop in some. Low level viremia in elite controllers is associated with some adverse consequences that are related to ongoing inflammation, but it's a very heterogeneous group. Some do not have CD4 decline or inflammation that would suggest that there's a problem. Adoptive therapy with broadly neutralizing antibodies has potent antiviral effects, really impressive. And even thinking about this as a potential therapy, you can make modifications to these antibodies, so that they have a dramatically prolonged half-life in-vivo. And the estimation is now that you could give a shot every four to six months with one of these cocktails of antibodies and that would be sufficient to keep adequate levels to control viremia. Which is I think really incredibly exciting. And the induction of both CD8 T cell responses as well as adoptive therapy with broadly neutralizing antibodies may be important components of a cure strategy. And so there will be more updates in the future, but I think we're at a really exciting time right now where there are these new modalities that are coming along. And really to bring this back full circle, it's really the connection between the people doing bench research like me, and the people like you that are seeing the patients, that are opening up these avenues. And that partnership is really critical to the successes we've had and to the successes that we hope to have in the future. So I really appreciate everybody's involvement in the studies that we've had ongoing. And I hope we can continue to keep you engaged and your patients engaged. So thanks very much.

[Video End]