

TPWKY

(This Podcast Will Kill You intro theme)

Erin Welsh

Hi, I'm Erin Welsh and this is This Podcast Will Kill You. Welcome to another bonus episode in this mini series of bonus content that we've been putting out over the past couple of months. If this is the first time you're tuning into one of these and wondering what this is about, I've been putting together these bonus episodes to explore in more detail one aspect of the topic that we covered in our previous week's regular season episode. I've also been using this opportunity to chat with people about their jobs, what they like about them and what they don't, how much they do changes from day to day, and any words of wisdom they may have for people just starting out in their careers. So far I've gotten to chat with some fantastic folks about hepatitis B stigma and discrimination, a new drug for human African trypanosomiasis, rabbit hemorrhagic disease virus, and it's been fascinating to see how wide ranging this work can be and how many different approaches can be used in the field of public health.

This week I'm taking a bit of a zag from last week's episode on multiple sclerosis by turning my sights to the Epstein-Barr virus, helped along by Dr Micah Luftig, Associate Professor and Vice Chair in the Department of Molecular Genetics and Microbiology at Duke University. Last week Erin and I covered multiple sclerosis which is a disease of many mysteries. Go and check out the episode if you haven't already. One of these mysteries which could be considered the central mystery really is what causes this disease. Recently a couple of studies were released that shed a bit of light on this aspect of multiple sclerosis, especially as it relates to the Epstein-Barr virus, a virus that has long been suspected to play a role in this and many other diseases.

In the case of MS, there doesn't seem to be one single cause for what makes some people develop this disease and it's likely many factors working together, such as a lack of vitamin D, genetic predisposition, a history of exposure to cigarette smoke, and Epstein-Barr virus. But it does seem as though EBV is probably a crucial part in the development of this disease. In our MS episode we talked about the implications of this recent research about EBV and MS and what it could mean for the prevention or treatment of multiple sclerosis. And that discussion, it also got me thinking just more about this bizarre virus, the Epstein-Barr virus and what about its biology has led to it being implicated in all kinds of cancers and autoimmune diseases beyond multiple sclerosis. So I wanted to use this bonus episode to get up close and personal with this extraordinarily prevalent virus. This bonus episode, it doesn't mean that EBV won't someday get the full Erin squared treatment in a regular season episode but who doesn't love a little sneak peek?

Since its discovery in 1964 for the Epstein-Barr virus has been implicated in an impressive number of different diseases, including various cancers and autoimmune diseases. Just as we found in our multiple sclerosis episode, there are still many mysteries and unanswered questions that surround the Epstein-Barr virus but over the years we have also made incredible strides in understanding how it does the things it does. One of the researchers who has helped to answer those formerly unanswerable questions is Dr. Micah Luftig. Dr. Luftig has graciously agreed to submit to my many questions, not just about the Epstein-Barr virus but also what it's like to be a professor. What other options are out there for someone interested in viruses and microbiology, favorite virus fun facts, and so much more. I'm going to take a quick break here and then I'll let him introduce himself.

TPWKY

(transition theme)

Micah Luftig

I'm Micah Luftig, I'm an Associate Professor and the Vice Chair here in the Molecular Genetics and Microbiology Department at Duke University School of Medicine. My lab studies EBV, Epstein-Barr virus. Primarily we've studied how EBV infects and immortalizes human B cells and that's a model for lymphomas in immunosuppressed patients.

Erin Welsh

Thank you so much for joining me today. I am so thrilled to get into the nitty gritty of Epstein-Barr virus. So what is EBV? Can you tell me a little bit more about this virus? What type of virus it is, how do people get it, and what makes this virus so special?

Micah Luftig

EBV is a herpesvirus. So it's in the family of, we currently know there are 8 human herpes viruses and EBV is like all herpes viruses, a large double-stranded DNA virus. And what that means is that its genome is made up of the same material as human genomes. And so that material is packaged up into a protein shell and decorated on the surface with glycoproteins which we've heard a lot about the news in the last two years. And this virus is complex because of its size. So it's about 170,000 bases long and it can encode about 80 different proteins as well as a bunch of little RNA gene products that help take over the cell. It's special because it has an intimate relationship with humans.

Virtually every adult on the planet is infected with EBV and you're infected when you're a child, usually in the first decade of life, the virus is transmitted by saliva. So it could be your mom or dad kissing you, it could be from another kind of kiss that happens in young age and usually the infection is relatively benign. But what happens is that the virus gets into the cells called B cells, which are the antibody-producing cells in your immune system, somewhere in your oral mucosa like your tonsils or adenoids. And when that happens the virus goes latent and that's really where the intimacy starts. The latently infected cell can harbor the virus more or less for your whole life.

Erin Welsh

Can you talk a little more about what's going on at the cellular level with EBV infection?

Micah Luftig

I keep bringing up B cells which maybe most people don't think about as much as I do but it's sort of an important cell type to think about because the virus has evolved clearly to take advantage of being latent and living in a B cell and mimicking how B cells normally respond to antigens. So because they're antibody-producing cells of the human immune system, their goal is to have an antibody on the surface of the cell that sees an antigen from some pathogen, get excited, the cell starts to divide and make better and better antibodies that ultimately are used to fight whatever that pathogen was. Well EBV sort of takes advantage of that process and has specific proteins that mimic the kinds of proteins that get activated in cells when they see antigen and drives that same process that B cell would have done if it had seen some foreign pathogen.

And so the end goal, I'm cutting to the chase here of why this thing is so successful and so amazing, is that the end goal is that the infected B cell that starts off in your tonsils or what have you ends up as a memory B cell in your blood which just sits there for weeks or months or longer. And the virus is completely latent. We can get into the nitty gritty of what the latent replication cycle is like because it's not the typical replication cycle you think of a virus where you make new particles and you get out, it's actually just the viral genome is circularized as an extrachromosomal piece of DNA. So you start with one, you wind up with about 10 in the memory B cell compartment.

But say an antigen comes and triggers that B cell to think that it needs to make a ton of antibody, that's a dead end for the virus and it switches to the lytic cycle which for EBV the way it happens is that these latently infected B cells antigen comes, reactivates it. Now you make thousands of particles that are released from the cell. That starts a life cycle of then the other phase which is in epithelial cells. So cells in the oral mucosa, when the virus gets out it will go in and instead of doing that whole latency dance that I just described, that sort of beautiful B cell latency dance, it just replicates like any other virus, the textbook example of it gets in, it replicates, produces tens of thousands of particles, kills the cell. And that amplification step is actually what's happening in all of us and why the virus is released into the saliva and getting out to be able to transmit to others but also to infect new B cells in your oral mucosa.

Erin Welsh

Okay, I see. And so in that initial infection it goes into the B cells and then eventually it will go into the epithelial cells when it is actively shedding virus.

Micah Luftig

Right.

Erin Welsh

Gotcha. Okay. And so many or even most people who get EBV may not ever know it because it doesn't produce any symptoms. But what about when it does? What are the symptoms of a symptomatic EBV infection? And what's going on at a cellular level that can lead to those symptoms?

Micah Luftig

I'll even step back and answer the question of why don't people get sick when they're infected with EBV.

Erin Welsh

Perfect.

Micah Luftig

Because it turns out that EBV latency proteins are exquisitely well recognized by the T cell response of the human immune system. And so in adults 1-2% of all of your T cells are specific for EBV proteins. They are activated and will eliminate those latently infected cells that are producing the viral proteins pretty efficiently for your whole life. And so it's only either in the case of immune suppression where EBV can cause problems in the B cell compartment and where you become much more susceptible to the lymphomas that EBV can drive, we can talk more about that in a bit. But where it causes disease though first so to speak in most folks' life is in the second decade of life. So if you're not infected in the first decade of life then it can be a problem because about 50% or so of those primary infections cause mono. So EBV causes infectious mononucleosis.

And the reason that happens is that the same dance of the latent infection in the B cells happens but the T cell response in fact is over exuberant and you will have on the order of half of all of your T cells in the blood will be EBV-specific for a couple of weeks. And that massive systemic expansion of T cells and the cytokines that they produce is what causes the fatigue and symptoms of mono. And there is a failure of those T cells to get to the tonsils, the oral mucosa where the EBV infected B cells are to shut things down in essentially anyone older than an adolescent, if it's your primary infection. And that's a great immunological mystery but the idea of having a vaccine that in individuals that are not yet infected that could potentially prepare your immune system to deal with that primary infection later in life could be something that prevents mono and that could have also further benefits down the road. So it's not the B cells that are infected that cause disease in mono, it's the massive expansion and failure of contraction really of the T cell response.

Erin Welsh

That is very interesting. So besides the age differences in terms of when you're first exposed to EBV, do we know anything more about what determines whether or not you'll have a response to EBV infection or primary EBV infection?

Micah Luftig

From the standpoint of everybody is going to be exposed to this virus, right, so the vast majority of people follow the course that we just described. But because so many people are infected, it turns out that there are genetic variants that families can have where the individual is not able to control that primary EBV infection in B cells because their their T cells are in some way unable to see and kill the infected B cells. And I say it that way because it turns out some of the biology and immunology that's been done on these questions actually detect not necessarily wholesale T cell immunodeficiencies but specific defects where T cells can't recognize B cells. And if they can, if there's either a transplant for example of hematopoietic stem cells or T cells that can come in to preserve that function, then they can eliminate the B cells. But the T cell response to other viruses may not be deficient.

So there is now an emerging recognition and field around what we would call chronic active EBV and that is an umbrella under which individuals that have for example exosome lymphoproliferative disease, XLP, which is caused by a couple of different mutations that can prevent the T cells from interacting with the B cells and other genetic variants that prevent T cell activation and T cell killing of the EBV infected B cells. And so then there can also be spontaneous or somatic mutations like happen for example in cancer progression, but in the immune system where those somatic variants end up causing an inability for T cells to recognize the EBV infected cells. And so in sum that that sort of umbrella of diseases that one could all lump together as chronic active EBV are what would lead to folks basically not being able to control EBV. And the consequences of that can be pretty severe but range from mono-like symptoms recurring but can be as severe as developing lymphomas or other EBV associated cancers.

Erin Welsh

EBV is involved with many different types of cancers. Can you talk a bit about how infection with EBV could lead to cancer development?

Micah Luftig

By the numbers of patients, EBV-associated gastric cancer is the most prevalent EBV positive cancer in the world. Almost 200,000 people. So about 10% of gastric cancers are EBV-positive and what that means is that not the person is EBV positive, the cancer is EBV positive. So every infected cell in the tumor has EBV in it. So how the heck could that happen? Turns out that EBV doesn't really like infecting epithelial cells on its own in the lab. Whereas if you take a latently infected B cell and you co culture it with epithelial cells that are uninfected and you reactivate the B cell, that triggers reactivation and transfer of the virus through cell to cell contact to the epithelial cells 1000 times more efficient than if you did a direct infection.

So piecing that all together and the fact that in gastric cancer you often have an underlying gastritis, sort of chronic infection, dysbiosis in some way that is a precursor to the cancer, it is very likely that EBV infected B cells that have an antibody on their surface with a specificity for some of the bacteria that might be causing the gastritis home to the basal lateral surface of the epithelial cells in lymphoid tissue underneath that and essentially are reactivated right in the spot for the virus to then infect epithelial cells. Now what I told you earlier was that when the virus infects epithelial cells by default it goes lytic, it just replicates and it kills the cells. So how would that cause cancer? That doesn't make any sense, right.

For viruses to cause cancer or contribute to causing cancer, they have to have something go wrong in their replication. And one of the things that needs to go wrong is that when it infects the cell, it has to have some aspect of its replication function crippled either by mutation or by the cell having heightened antiviral responses or some other breakdown in replication. And so in EBV-positive epithelial cancers, the virus is actually latent. So it's an aberrant process, right. Instead of replicating lytically, it accidentally finds itself latent and some of the latency proteins can be made, not all of the ones I described in the B cells but usually those membrane proteins that keep the cells alive, the pro-survival proteins, they're usually expressed and then the EBNA1 protein that maintains the viral genome is still expressed. And together that cooperates with cellular mutations that arise in driving in this case gastric tumorigenesis.

Erin Welsh

We know that this is a global virus, 95% of people have it by the time they are adults. But is there geographic variation in this virus? Are there different types of EBV? How much genetic variation is there in this virus?

Micah Luftig

So most double-stranded DNA viruses like EBV or other herpesviruses compared to other viruses are relatively stable genetically. They really don't mutate that much like influenza virus or SARS-CoV-2 or any of the sort of acute respiratory viruses. Those RNA viruses don't tend to have the proofreading capacity typically in their polymerases when they replicate. And so they throw in errors every couple of 1000 bases of nucleic acid. Whereas it's a much lower error rate in DNA replication for double-stranded DNA viruses. That being said, now we know as of about maybe 7 or 8 years ago with genome sequencing technology developing and becoming cheaper. So we now have a couple of 100 genomes sequenced and what's emerged is a couple of things.

So one is that the prototypical genomes we've been working with are representative actually of what you see across the world, so that's good. We know that there are two major types of EBV, so type 1 and type 2 is what they're called. And they vary in very specific genes which is primarily the latency genes. So the majority of EBV in the world is type 1, it's distributed across the world. And type 2 is more prevalent in Africa and in some parts of Asia. And so in some ways they're almost like two different viruses but as far as we know they really operate very similarly in terms of B cell infection and latency and reactivation and everything else.

So the other things that we learned from the genome sequencing experiments are that the genes that are important for virus entry for example that could be vaccine targets are relatively well conserved. So there's probably not a big concern about that variation like you have for flu for example in hampering vaccine design. But there is some variation. But coming back to the geographic distribution, it turns out that one of the latency genes called LMP1 or latent membrane protein 1, it varies quite a bit relatively and one can see geographic distributions that link a particular LMP1 genotype to regions of the world. We don't know what that means in terms of disease or spread or what have you but it's been observed.

Erin Welsh

So let's get into latency. Tell me more about what's going on with latency. What does it mean for a virus to go latent and what can trigger reactivation?

Micah Luftig

Yes, awesome. Okay. It's my favorite topic. So latency in the case of EBV is sort of an active latency. It's not the kind of latency you might think of as the virus is sleeping and don't wake it up. It is a form of infection in B cells that is the default form that when you acquire EBV in the saliva, the initial infection in B cells leads to a series of 8 viral proteins being expressed and they're called latency proteins. 6 of them are transcription factors so they go into the nucleus and they turn on genes and turn off genes in the host genome, and 2 of them are membrane proteins at the cell surface that activate cellular signaling pathways and that mimics how that B cell would normally have responded to antigen or a foreign pathogen if it were normally doing its job, but EBV is sort of co-opting that. So when the latency proteins are expressed the cell that it infects, a B cell is just a resting cell, it doesn't divide unless it gets signals to divide.

And so those nuclear proteins, the so-called EBNA, Epstein-Barr nuclear antigens, when they are expressed the cells will start dividing and they actually do so very rapidly. And that's mimicking what happens when a B cell would normally have seen some foreign antigen. And so that rapid proliferation occurs for a number of divisions. And at the same time these membrane proteins that are activating the signaling pathways are telling the cells, 'At all costs, stay alive'. And the reason that's important is that the process from a naive B cell maturing to becoming a plasma cell or a plasmablast which is one of these antibody-secreting B cells or a memory B cell, that process is one in which the B cell is activated and rapidly proliferates. So you have a lot of B cells around to ultimately be able to make antibodies to stop some pathogen from taking over. And in that process it's a little sloppy. So an enzyme comes on that actually damages the DNA, cuts the DNA, it causes mutations in the DNA in the so-called immunoglobulin locus.

So the genes that are gonna make the antibodies get mutated and that is the selection process by which the B cells go from having an antibody that initially recognized the pathogen to making a better and better, higher affinity antibody. That process is dangerous, right. There's all this DNA damage, there's all this churn and everything. So EBV actually mimics that process. And so if that cell is going to stay alive and still be an EBV infected cell when it comes out of it, it needs to tell the cells not to die. And then after a couple of rounds of division it gets out into the periphery, into the blood as a memory B cell and it shuts everything off and it becomes truly latent and quiescent. And the reason it does that is that all of those proteins that I told you about, the EBNA's and the membrane proteins, so-called LMPs, those are highly immunodominant and T cells are going to recognize them and kill those EBV infected cells.

So it shuts everything off, gets into the blood, and sits there. When that cell divides it makes one protein. And the one protein is a protein called EBNA1 that can facilitate the DNA replication just of the EBV genome which is actually represented at this point as probably 8-10 copies, so extrachromosomal circular copies of EBV DNA. And then partitions them to daughter cells. Then if those cells find themselves in lymphoid tissue in the oral mucosa and the actual antibody on the surface of that B cell recognizes an antigen, that triggers the differentiation of the cell and the switch to lytic replication. And so then the virus makes tons of particles and gets out. Now it turns out that's not the only way it can happen. Like most herpes viruses we often say stress can induce reactivation. What is stress? So DNA damage from radiation as a stress, hypoxic environments or low oxygen environments as a stress. In fact some small molecules that are secreted by bacteria that might be in our oral microbiome as a stress can reactivate latent EBV.

So it's not just the B cell receptor or the antibody on the surface of the B cells that needs to signal or recognize the antigen to trigger reactivation, all of those different kinds of stresses can do it. A lot of this comes back to the idea that EBV is latently in all of us in our B cells and because it's in our B cells those cells have a very specific function, which is that they have antibodies on the surface and those antibodies could recognize other pathogens, they could recognize autoantigens, they could recognize nothing. And if they recognize nothing that cell should have died but EBV keeps it alive. And so that sort of central principle is what underlies the relationship between EBV and I think some of the cancers it's associated with, probably autoimmune diseases, and certainly how this symbiosis between EBV and the B cell, why it works basically. So about 1 in 100,000 of our memory B cells in our blood at any given time is EBV-positive. So that ends up being probably tens of thousands of cells.

And each of those cells has a different specificity. The B cell receptor on the surface of each of those cells, they might be for an E. coli in your gut, they might be for the cold virus you had when you were 4, they might be for a tetanus vaccine antigen, they might be for some autoantigen. But because the virus is quiescent most of the time, everything's fine. So when we talk about EBV flaring up and this kind of thing, EBV is a barometer of our humoral immune response. It's like a little gage of when things are okay and when things are imbalanced. And that's vague but you can imagine that you could put specificity on it if for example it was a particular pathogen driving a particular clone of EBV that mimicked an autoantigen. Maybe that's what causes Sjogren's syndrome sometimes or maybe that's what promotes MS sometimes, right. It's all about the B cell.

Erin Welsh

Talking more about autoimmune diseases and the potential role of EBV, what are the conditions that seem to have the highest support for an involvement of EBV? And is it sort of that mechanism that you described or are there different mechanisms that are involved?

Micah Luftig

I think there can really be likely two mechanisms. One is what I just described which is that because EBV finds itself in B cells, that's where it lives, if one of those B cells has an antibody on its surface that is autoreactive and that autoreactivity is pathogenic, then that would be a mechanism where the process that I described of how EBV latency proteins tell cells to proliferate, keep them from dying, expand clones, that cell may actually come back through the lymphoid tissue and need to expand again. And if that happens, EBV there to keep it alive. And so for example that's something that goes awry in Hodgkin's lymphoma. In this case it could be, in the case of certain autoimmune diseases, you can have B cells that are infected with an autoantibody, they expand and perhaps they expand to become plasma cells that go to the bone marrow and just secrete antibodies for a long period of time. And that could be just a pathogenic autoantibody that you need to get rid of because that's what's causing a particular autoimmune condition.

So that's one possible mechanism for how EBV could be involved in a variety of autoimmune diseases. Another is what was proposed in the recent Nature paper about EBV's association with MS and molecular mimicry. What they found was that if they looked in the cerebral spinal fluid of MS patients where B cells should not be hanging out but they found some, enough to be able to then isolate them and pull out the antibody genes that are in each individual B cell, express them, so make them in vitro in the lab, and then ask what are these antibodies buying? And what they found was that about 30% of patients had antibodies that reacted with EBV antigens. And when they drill down into which antigens were recognized, more often than not it was this viral protein EBNA1. And that protein is known to play all sorts of games to avoid the immune system.

So what does that mean? Why does that cause that? Why would that or could that cause MS? And it turns out that the small peptide region of EBNA1 that's recognized by the antibody is virtually identical to a region of a protein that's expressed in neurons called GlialCAM. And that indicates that that specificity is one where just one amino acid difference is enough to shift you from recognizing a pathogen to recognizing your own protein. And so I think those are the two favored and plausible mechanisms. Is it the EBV-positive B cells that are playing a role here or is it this other mechanism of molecular mimicry where the antibody response to an EBV protein could end up being what triggers reactivity with your neurons which is bad? The question of how much in every case of MS or any other autoimmune disease does this contribute?

I think that the serum in MS patients from the large military study is the strongest evidence yet of the requirement of EBV infection for developing MS and I think that the Nature paper really strongly supports a potential pathogenetic mechanism of molecular mimicry that could support the development of MS in some individuals. I think the idea that preventing EBV will prevent MS is going to require doing that experiment, right. But I think the chances of that preventing MS are low. It may be that a subset of MS is EBV driven in some way or it really does require continued EBV infection. And again, whether it's related to how strongly you're able to prevent autoreactive T cells and B cells from developing versus how well you keep your EBV in check, that's something that the field is really deeply interested in figuring out over the next 5-10 years.

Erin Welsh

So besides this MS research that's been in the news lately, EBV has also I feel like made headlines for its potential involvement in long COVID. What do you think about that? What research has been done on that? And do you think that it's a plausible link?

Micah Luftig

I think that the link between EBV and long COVID likely has to do with this idea that EBV infection, latent infection in B cells, is sort of a barometer of your humoral immune system. And so when things are a little off balance either because you've got a co-infection and a huge amount of cytokines being released either systemically or locally in some lymphoid tissue, that this can trigger EBV reactivation and depending on how well the patient is doing in terms of maintaining their EBV-specific T cell responses and EBV immunity, that can essentially be a mono-like situation or in any event can cause a lymphoproliferation and ultimately some disease associated with that that could overlap with some of the long COVID symptoms, so I think fatigue being the major one that has been linked. When EBV DNA is detected in the blood, that indicates that there's really a significant imbalance in these EBV infected B cells. And so whether that is again simply a barometer of the underlying immune health of that individual or is contributing to some of the symptoms like fatigue in long COVID I think just warrants further study.

Erin Welsh

So I want to end part one of this interview with a question that is very general and hopefully very fun. Do you have a piece of favorite trivia for either EBV or just viruses in general?

Micah Luftig

Yes. Okay. EBV was discovered in 1963-1964 by Anthony Epstein who was an assistant professor in the UK and his graduate student Yvonne Barr. And he had seen a talk in '63 from Denis Burkitt who was an Irish missionary surgeon working in Uganda who had characterized this large jaw tumor that is the most prevalent pediatric tumor in Sub-Saharan Africa. And at the time we knew that other animals could be infected with certain viruses that cause cancer but no human tumor virus had been discovered. And so Denis Burkitt presented this study where he mapped the epidemiology of this cancer, this Burkitt lymphoma across Africa. And it was almost coincident with where malaria was holoendemic.

Epstein was rapt and was certain that there was a virus probably transmitted by the mosquito that was also transmitting malaria that would cause this lymphoma. And so they set up a collaboration where specimens from the lymphoma will be sent from Kampala to London. And over months and months of investigation, no virus was found. And so the 26th biopsy was being flown to London and there was fog in the city and the flight was diverted to Manchester. And the sample sat overnight and was brought to the lab and the liquid that it was in was cloudy. And so he thought, 'Oh gosh, it must have been contaminated with bacteria but let's take a look anyway'. And when he looked under the microscope he saw that the cloudy stuff wasn't bacteria but it was cells. And some cells had sloughed off of the tumor and at the time nobody knew how to grow lymphocytes. So there was no culture system for lymphocytes.

But nevertheless Yvonne Barr tried a bunch of different conditions and was able to successfully grow the cells that had sloughed off from the tumor. And a couple of weeks later they had enough cells and sure enough in about 1 out of 100 cells, chock full of herpesvirus-like particles. And that was it, that was the discovery. And he got up and went outside and walked around the building and came back and looked again. And sure enough the cells were chock full of herpesvirus-like particles. So he was wrong about what kind of virus it would be, it wasn't transmitted by mosquitoes, but he was absolutely right that there was a virus in those cancers. That story of the discovery of the virus as told by Anthony Epstein at the 50th anniversary of the discovery about 8 years ago is my favorite piece of virology trivia.

Erin Welsh

That is such a fantastic story and it must have been so cool to get to hear it directly told by the man himself. So we're going to take a quick break here and then when we get back, I want to hear all about what virology as a career is like and any words of wisdom you may have for people who might just be starting out on this journey.

TPWKY

(transition theme)

Erin Welsh

Welcome back, everyone. All right, so let's talk about virology as a career, what it's like to be a virologist. What got you interested in EBV? Did you know all along that you wanted to study viruses?

Micah Luftig

I knew I wanted to study viruses and I was always interested in studying viruses that caused cancer. So it turns out my dad's a virologist which is maybe not the most common route that people get into the field. But in my case when I was a kid I used to go to American Society for Virology meetings on college campuses in the summer and hang out and eat pizza and meet graduate students and then meet virologists. And then as I got older I would go as a high school student and I started getting into the science, I was always a math and science nerd.

And so I really became interested in the biology and started to ask questions at these meetings. And then late in my high school career had some experience in doing some microbiology research. And then when I started in college I knew I wanted to work on viruses and so I found the virology lab on campus and actually it was a herpes simplex virus lab. So I started working with HSV from early on and how the virus enters cells and the glycoproteins it uses and the receptors and this kind of thing. And so my junior to senior year transition, I worked at the CDC. I had an opportunity to do an internship there and worked in the herpesvirus section with the chief named Phil Pellet. The lab was studying all different herpesviruses and around that time a new virus have been discovered called KSHV or Kaposi's sarcoma-associated herpesvirus.

And so they were really keen to just understand the basics, like let's grow this virus and let's purify it and let's figure out what proteins are in it and how it enters cells and all this basic stuff. And so I had a hugely impactful experience there, not just from the science and the kind of science we were doing but Phil, after we finished in the lab, would would stay and chat about the future, what I was going to do and where I might be interested in going to graduate school and what questions to work on. And I really had an opportunity to think about that carefully. And so he suggested EBV. He said if you want a big challenge and you want to understand viruses that can cause cancer, you should work on EBV. There are a number of labs in the country that were really exceptional studying it. So I wrote to them and applied to graduate schools and ended up going to graduate school to work on EBV basically.

Erin Welsh

So as a professor you have to do so many things, that one word covers a lot of different responsibilities. You have to teach, you have to write grants, you have to do the research, you have to manage a lab, you have to advise grad students, and everything inbetween. Are there any parts of your job that you absolutely love or parts that you could easily give up and not look back?

Micah Luftig

The part that I absolutely love is what got me into it from the beginning and it's seeing new data and seeing new discoveries made that no one's ever seen before, right. So that bug, that sort of fire in the belly to be able to see this new discovery and want to ask the next questions and figure out the mechanism and just develop a project, that's really what I love. And like you said though along the way, all of the other benefits, features of being a professor come with you and I have to say in my training I did not have an opportunity to do as much mentoring as maybe others. And that is something that I do really love, I love doing that in the context of the lab, sort of training graduate students or undergraduates that come in the lab, postdocs and also doing that in the context of faculty mentoring, really helping junior faculty get started and transition through tenure and all of those challenging spots in their career.

And teaching is something that I love when I'm doing it but I don't love thinking about having to do it. I'm telling you about a lot of things. What do I hate about this job? I've been thinking a little bit about that. I don't hate writing grants, I actually think writing grants are really useful as an exercise to distill your ideas into a digestible set of future experiments and setting up rationale for why you're doing what you're doing. I don't like the process of waiting and having it reviewed and biting your nails and all that stuff. But I do like writing the grants because of what it does for the science.

I don't love where things are right now with academic publishing, I think that could be improved in a number of ways. I think that one of the aspects that a lot of folks talk about and I agree with this is that really linking our sort of productivity and our worth to the impact factor of the journal that we publish our papers in is not not appropriate and how to get away from that when we evaluate faculty candidates or people coming up for tenure promotion or what have you is tough. But I think we try our best to do that in terms of evaluating the actual impact of the work and the rigor of the science and the reproducibility of the science which often isn't something that comes into play despite how challenging that issue can be. So I think if there was one area that I don't love, it's kind of this space of navigating the publication system.

Erin Welsh

So on the alumni section of your lab website, I see that you've graduated students that have gone into very different careers from government positions to industry to medicine and others. So besides academia, what other careers do you think that a Masters of Science or a PhD in microbiology would set you up for?

Micah Luftig

Yeah, absolutely. I think a lot of different careers. I think that we train critical thinkers, we train effective communicators, we train folks to solve difficult problems by working in and valuing diverse perspectives on teams that will get you there. And that skill set describes, as you can imagine, a lot of different industries, right? So you obviously are learning how to do that in the context of pipetting and whatnot. So doing that in science, in industry, is the most logical place to go next from the point of view of if you love the science aspect of it. If you love the communications aspect of it or if you love the entrepreneurship aspects of it then there are sort of slightly different paths that you can take. So the industry now, it's interesting. When I think back to even my time as a postdoc, the opportunities and industry were relatively limited to sort of Big Pharma or basically big biotech or startups but the relative risk there was still pretty high.

And that array of opportunities to be a PhD or Masters level scientist in biomedical research in industry is now incredibly diverse and it's not restricted only to Boston and the Bay Area, RTP, where we are here obviously, it's full of companies developing all through that spectrum. So I think a lot of folks are really excited about moving into industry where they can sort of see the kinds of basic discovery-type work we do here translated into drugs or therapies in some way. And when you're there you have an opportunity to really expand and explore other aspects of that process, right. So whether it be liaising with clinicians as a medical science liaison, whether it be developing, writing NDAs and doing really more science communication or having an opportunity to shift and do more business development and entrepreneurship. There are a lot of opportunities just in what now is kind of biotech and pharma, that really broad industry.

And then like you said, some of the folks from my lab have gone on to policy fellowships and and really working to impact the way that our government and any level really thinks about and communicates science and I think that's obviously very much needed these days. And I think there are certainly still other areas that you're competitive for, consulting or patent law or what have you. So really a wide range of opportunities in what you can do with a Masters or PhD and the sort of resilience and other things that come from doing your PhD really set you up nicely for any of those kinds of careers.

Erin Welsh

What advice would you give someone who is interested in biology broadly but isn't sure exactly what they want to do or what's available to them? And what do you think are the most important factors to consider when thinking about the career that you want to have, whatever it relates to in biology?

Micah Luftig

Yeah. So I think even starting to think about this at an early age, high school or even before, I would say seek out a mentor, seek out someone that you can talk to about science, about being a scientist. There are a lot of, especially in the COVID era, a lot of societies like ASB and ASM have been doing really open webinars and podcasts and communication events to encourage young people that are interested in biology and interested in science to come not just learn about what science we do in the lab every day but what the field really is like and what the path is going to look like, right. Because I think a lot of folks don't know what for example graduate school is like from high school or even college. It's like some people think it's just the alternative to medical school or something.

Whereas what I would suggest is that if you can find a scientist, try to find an opportunity to do research in some way, there are more and more even virtual options for this because of what's happened with the pandemic where you can engage with the scientists in the lab and maybe do a computational project or just reading and learning about a topic. And ultimately I think what you want to try to get to is to be involved in doing an experiment and seeing the discovery. If that bites you, if you see something no one has ever seen before, whether you did it with your own hands or you're working with a graduate student or somebody in the lab and you see something and if that bites you and you realize oh, I could do this and see things nobody's ever seen before and really develop that and come up with new experiments to test new hypotheses, that is when you know that being a scientist might be for you.

Erin Welsh

So you talked about one way that you wish academia could be better, right, and in the context of publishing and the way that we evaluate certain candidates or the way that people maybe evaluate their own self worth in academia. What would you say about grad school? What are the ways that in general graduate school in biology or microbiology could do better?

Micah Luftig

Graduate school is changing a lot in front of our eyes. When I got to Duke about 15 years ago, most of the programs I would say were relatively conservative and kind of old school in their approach which was the mentality that students were workers that had to have pressure sort of applied to have them perform and produce things. And that is for obvious reasons the kind of thing that leads to really significant burnout and mental health challenges that certainly still exist in graduate education today. But I think what I'll say is a number of things that happened over the years at least here at Duke where we've recognized a lot of how we were training students and basically blind spots in what we were missing, especially in terms of what we were just talking about before which is where are you gonna go, right? Are you going to go into academia? Are you gonna go into industry? Are you gonna be a scientist? Are you gonna have a different career path?

And when you simply look at the numbers, you see that about 15-20% of our graduates wind up in academia and 50% are in industry, right. So at the time people would say alternative careers or something like that to academia which is ridiculous, right. The majority of people are going into other careers. So it was that realization that happened maybe 10 or so years ago here at the graduate school, a lot of effort was put into rethinking, reimagining graduate education around having a PhD, what you need to be trained for in the biomedical research workforce and what are the skills that are the most important broadly. And number one is problem solving, creative thinking, resilience, communication to a broad audience, to a narrow audience, writing.

All of these things really are the foundation. Being able to do this in an environment that is respectful, diverse, pro-student. But it's just a rethinking of what the goals are and how you get there and I think partnering with one another. It's a mentor-mentee relationship but it's also one where we're colleagues, right, and seeing each other in that way and being respectful and challenging each other, right. I mean that is part of the process but in a respectful way.

Erin Welsh

I have one last question for you and that is to ask you what you hope this next year brings in terms of EBV research or other research or just general personal goals for you or for your lab?

Micah Luftig

So for the lab, I'm really excited about the area of science that we've been in for a couple of years now which I would generally call a heterogeneity of infection. So if you infect cells, they don't all behave the same way. So we generally lump things together sometimes and say 'infected' and 'uninfected' or that kind of thing. And I've always been really interested in temporal dynamics like how things change over time after infections. But also what's the difference between cell A and cell B and if you infect a million cells, are they all responding the same way? The short answer is no, not at all. And so we've been using technology called single cell RNA sequencing as one method to be able to see those differences, whether it be during latency or lytic reactivation of the virus or in different tumor cell lines and different settings. And we've published a paper on this already and have a couple more coming out this year that are really telling us just about how different the outcomes of viral infection can be at the single cell level and what that might mean then for disease, for latency establishment, for therapeutic approaches. And I think it's really an exciting time to be studying EBV. As you know, the first doses of the Moderna EBV vaccine have gone into arms and so everybody's excited to see how that does in terms of impacting mono and also uh EBV replication and development.

TPWKY

(transition theme)

Erin Welsh

Thank you so much, Dr. Luftig. That was such a fascinating interview and I definitely gained a lot more respect and awe for this virus and what it can do. If you would like to learn more about the super cool work that Dr. Luftig and his lab is doing, I will post a link to his lab website on our website thispodcastwillkillyou.com. Speaking of websites, our website is also where you can find all kinds of things, like the sources for all of our episodes, transcripts, quarantini and placebo recipes, our bookshop.org affiliate account, links to music by Bloodmobile, links to merch and Patreon and so much more. Thanks again to Bloodmobile for providing the music for this episode and all of our episodes. And thank you to you, listeners. I hope you enjoyed this foray into EBV. And a special thank you to our wonderful, generous patrons. We appreciate you so much. We have got a brand new episode on a brand new topic coming out next week so until then, keep washing those hands.