Episode 42 – Mia Huang: How sugar biology can help diagnose and treat cancer

Drew (00:03):

Greetings and salutations listeners. I'm Drew Duglan, and this is Science Changing Life. Today we take a look at very important sugars in the body called glycans, and this whole field of study known as glycobiology. I'm joined by glycobiologist Mia Huang, who is determining how these molecules might be tweaked to help stop the development and spreading of cancer. First, though, let's join Mia as she recounts her earlier PhD and post-doc work on the ability of different animals to produce natural antifreeze agents.

Mia (00:33):

So there are these natural antifreeze molecules called antifreeze, glycopeptides, or antifreeze peptides that allow these organisms to survive in sub-zero temperatures. What's fascinating about these molecules, however, is that they actually have groups on them that allow them to interact with nucleated ice, and when they interact, they prevent the growth of that ice crystal. And so if you dissect, uh, a fish or an insect in the, in temperatures and open up their blood, and you'll actually see these tiny little crystals, but in a natural environment, you'd expect these crystals to grow into large pieces of ice and, you know, disrupt the organs of, um, the animal. But because they have these antifreeze glycopeptides on them, these ice crystals just stayed really small. So we call those ice inhibiting agents and the idea was, hey, we have these new sets of molecules that are much more robust than a normal molecule. Could we convert them into natural antifreeze that we could use to, let's say, preserve organs or tissues?

Drew (01:34):

Wow. I was gonna ask, are those antifreeze agents at all related to the type of antifreeze you put on your, uh, your car in the winter?

Mia (01:42):

They're much more sophisticated, but essentially they use the same principles, hydrogen bonding, but there's a little bit of an element of molecular recognition as well, the shape of these molecules. So the antifreeze that you buy from the car dealership, they rely on the same chemical principles, but they may not exactly have the same shape. And so you need large amounts of these materials to actually see the anti-freeze effect that you're trying to see. But in these animals, they're versions using the same chemical principles, but with a little bit more sophistication in terms of molecular recognition, they can get much more anti-freeze activities.

Drew (02:19):

And now in terms of understanding, uh, other biomolecules, I believe now you are an expert in glycans in your lab. So can you tell us about what glycans are and sort of their general importance?

Mia (02:32):

Yeah, and so that actually, what were the kinds of thinking that led me to my current projects. What's the purpose of these glycan molecules on these antifreeze glycopeptides In that sense, they were only being used to sort of in, uh, interact with ice crystals, but it got me thinking about what these molecules are, why would nature ever bother to make these molecules? And then it turns out they are serving really important recognition properties, just like DNA and proteins are in the cells. So these glycans exist

in virtually all animal cells. In fact, they actually coat the cell. And in fact, the collection of all of these glycans that the cell surface is called the glycocalyx. So we think of glycans typically as like a carbohydrate type of molecule. You eat them for nutrients, but I'm, I'm interested in studying them on the context of this molecular recognition property.

(03:23):

And so they're at the cell surface, for example. And so you think of them as the first point of contact with an incoming pathogen like SARS-CoV-2, another cell trying to communicate with your cell. Those kinds of communications are facilitated or they at least have to negotiate through what these glycans at the cell service are doing. And so I'm trying to extricate a lot of these biological functions, provide new tools on how to study them in the hope that these kind of molecular understanding can help us discover new ways of fighting glycosylation mediated diseases. And it turns out there's a whole suite of biological systems that are already related to glycosylation and these glycans.

Drew (04:05):

Is it true that, uh, blood type is from these types of sugars on our cells?

Mia (04:10):

Yeah, your red blood cells, well, depending on your blood type, um, uh, all of these red blood cells, like I said, are coded with these glycan molecules and the fact that you're a, uh, gly, uh, blood type A or a B or O, um, all has to do and they're all classified by the type of sugar molecules or glycan molecules that are on your red blood cell. And that has important implications for blood transfusion, for example. And in fact, one of the sort of newer engineering ways on how we can make use of that information is to create a universal blood type where we can engineer all red blood cells to have the same kind of, uh, or a non-immunogenic kind of, uh, glycan so that everybody can use them. And we wouldn't have to potentially go through all of this typing that we do now to make sure that there are no adverse immune reactions.

Drew (05:01):

Oh, wow. And I guess that's one of the main issues with organ transplants too, right?

Mia (05:06):

It is, exactly. Yep.

Drew (05:07):

Wow. Oh, that would be so cool. So do we know how many types of these different glycans there are in the body?

Mia (05:14):

<laugh>? Wow. Um, that seems like a easy question, but it's actually quite difficult. Oh, <laugh>. So because there are, on a theoretical level, there's about 40 kinds of monosaccharide precursors building blocks, but in general, majority of the glycans in the cell are made up of nine particular monosaccharides, but they all inter convert towards each other. There are these enzymes in the cell that convert one monosaccharide to another, and it essentially greatly amplifies the amount of building blocks that are present. So it's not only the building blocks that cause the diversity, but the way they're linked towards each other as well. So each monosaccharide has at least four to six sites of modification and how you link one versus the other can have important implications as well. So like a, a really popular

example is the influenza virus that causes the flu and humans in their lungs have one particular kind of linkage in their sugar glycan coating, whereas pigs have another. And so if an influenza virus has a protein that likes to bind one kind of particular linkage, then it can only affect a human or a pig. But if you now have a mutation in the influenza, which it actually does happen, that it allows them to jump from the pig being able to infect pigs only towards that versus humans. So we pay a lot of attention to the chemistry of these sugars as well.

Drew (06:38):

Are there specific diseases of glycans?

Mia (06:42):

Yes. So glycosylation, the process of installing sugars is generally a really important process, is essential for life, but defects in this machinery can lead devastating diseases sometimes are called rare diseases. And so people or patients that have these generally don't have long lifespans. And so a lot of them have defects in the enzymes responsible for making glycans or breaking them down. This is a normal process of how the cell behaves. What's really got me excited was that there was this enzyme replacement therapy that allows, uh, essentially synthetic enzymes to be supplied to patients that were lacking a functional copy of this enzyme. So you think of maybe a, you know, a mature person having this disease and you give them this enzyme and that corrects their glycosylation. But the study that was published in New England Journal of Medicine showed that this therapy could also be applied in utero and help babies develop into a more healthy version because they have this particular enzyme now supplied.

Drew (07:48):

So you could screen for the defects in the sugar molecules, then administer this synthetic modified form that could reinstate the normal pattern of development.

Mia (07:58):

Exactly. Uh, what's kind of another kind of intersection with media is, um, there's this movie in the nineties called Extraordinary Measures. This was a movie by Harrison Ford. Harrison. Ford now is playing a real life….

Drew (08:12):

I love Harrison Ford!

Mia (08:13):

<laugh>. And so he was, um, in the movie, he plays his frustrated scientist that was like exploring this biological pathway, um, to help patients with this congenital disorders of glycosylation. And he, he met patient advocates, parents of, uh, patient that had this disease and they reinvigorated this scientist. And this particular scientist from the University of Nebraska is actually largely responsible for creating avenues for enzyme replacement therapy.

Drew (08:42):

And so scaling that up even further, which organs do you think are easiest to make synthetic or where do you think we'll have the best success with this tissue regeneration?

Mia (08:52):

I think the red blood cell is probably, probably the one that's easiest. Red blood cells are much easier harvested and manipulated. There's a lot of red blood cells. I think the gold bar here for what I'm describing is probably neurodegenerative diseases now, one, collecting healthy versus disease versus, um, differentiated cell types. And being able to compare all of the glycosylation profiles of these cells is challenge. We need sufficient amounts, we need large amounts from different populations to be able to understand what that universal code might look like if there was one. So the sample scarcity is one barrier to this problem. But I think there are also, for the neuronal part, the relationship between neuronal synapses, you know, that's what we expect neuron to do. So carry electrical information essentially, and the link between that and glycosylation is still really, uh, poorly understood. So I see that as sort of the higher end of what the ultimate goal might be.

Drew (09:56):

Got it. So glycans are a major player in sort of the immune system, right? And the immune system sort of targeting towards cancer. So can you sort of speak to the role of those sugar molecules in cancer development and some of your work in this space?

Mia (10:13):

Right. And so I also, um, I would be remiss to mention that the Nobel Prize in chemistry and this year was awarded to this professor called Professor Carolyn Bertozzi. And she, 20 years ago, 30 years ago, glycoscience was not as popular as it was now. And a lot of it has to do with what Professor Carolyn Bertozzi has done for the field, which is to provide us tools to understand what these different glycosylation patterns might look like on cells, but also to create avenues on how we can manipulate them. So there was previous data describing that healthy cells versus cancer cells exhibit different glycosylation probes. Again, we start from correlation. And then other people have found that these extra glycans on cancer cells help them evade immune responses. So it tells the body to, uh, shut up. Um, we're, uh, we are like your own cells don't touch us and allows the cancer cells to proliferate.

(11:11):

And what she's done recently is to create an antibody that targets your cancer cells specifically, and then this enzyme can clip off these extra sugars. And now not only do you have a drug that targets the cancer cell, but it also removes the signal that tells the immune system to shut up. So it's like a double edged sword. You target your cancer cell but also expose them towards the immune system. And so it, it's going, this is going to be a new way of, um, much more selective therapeutic avenues to treat cancer. So generally my work is involved with profiling, developing techniques to pro profile glycosylation on different cancer cells, understanding the causes of why this extra glycosylation exists, what is it doing to help cells differentiate, helps cells evade, um, the immunity, and then being able to create pathways to target that pathway as well.

Drew (12:06):

Can these sugars be used as diagnostics as well? Like, oh, we've found this certain, uh, sugar change on this cell or, or in the blood or what have you and Oh, this could be a red flag for possible cancer progression?

Mia (12:20):

Absolutely. People have been talking about using glide cancer as biomarkers for a long time. What has re-energized this field is the addition of AI into the equation. And so because these glycans in cancer are

so complex, it's diff very difficult to predict. Now the infusion of AI into glycoscience has allowed us to say, Hey, are, are these correlations real? Can we expand them towards a larger set of populations? So there are these new companies now that are making proprietary, uh, software based on what they're finding profiling glycosylation from different patients, healthy versus cancer, what kind of grade of cancer, and then use AI to make sure that these correlations are robust and then use them as diagnostics.

Drew (13:08):

How do these glycans change then when, uh, a cancer metastasizes and then sort of infiltrates other, other organs?

Mia (13:17):

That, that's also really interesting. So if you think of yourself as a cell and you have this outer protective layer of sugars on them, that sugar layer could either help you as a cell stay where you're at like a solid tumor, or you can imagine changing your outside coat and allow you to lift yourself up and then move to a different spot. So just like metastasis. And so we've found that changes in the glycocalyx composition is responsible for or correlated to the ability of cancerous cells to either stay, put a cell tumor and grow where they are and even maybe supercharge their growth, but also allows them to metastasize towards different areas. That's also one area where people are actively exploring maybe not allowing the cancer cell to metastasize towards different areas, is enough of a therapeutic strategy again, by changing the glycosylation.

Drew (14:13):

And then when I think of different carcinogens, so you know, whether it's smoking or different chemicals or radiation, I mean, is that all acting at the DNA level to cause cancer or are those directly acting, do you think on these glycans too?

Mia (14:30):

Well, they could be also directly acting on the genes that are responsible for making glycans. So that's definitely possible and we have seen that as well. I think the one consequence of how we conduct science these days is that you're either a geneticist or a biologist or a biochemist or you're a glycoscientist. And we're not sort of telling the story in a, a more holistic way, but yes, in terms of, you know, looking at cancer in response to different environmental stressors, we see changes in glycosylation and, you know, uh, person A knows that as a glycoscientist, person B knows that from a genetic level, it takes a person C to connect that information and say, Hey, that change in glycosylation is because your DNA now has changed. Right? So yes, those are all connected.

Drew (15:14):

All right. So we're moving out of the, the lab then. How else do you like to spend your time when you're not, uh, researching these glycans? And I believe you have some travel coming up.

Mia (15:25):

Yes, yes, yes.

Drew (15:26):

Tell us about that.

Mia (15:27):

Okay, so I got invited to be a keynote speaker for the Australian GlycoScience Symposium. Um, so I'm, I'm really staked about it. I'm getting to meet people that, uh, I only know about on Twitter <laugh> based on their work <laugh>. So that's a kind of exciting. Um, but apart from the lab, I, I like to play with my dog, her name is Rosi, for Rosalyn Franklin, um, but also play a lot of video games. Unfortunately, that's like my, uh, mind numbing activity.

Drew (15:58):

What, what kind of games do you like? What kind of styles?

Mia (16:01):

Games? Um, I'm playing Civilization five at the moment, not six.

Drew (16:05):

Is that one of those where you're kind of like building, uh, cities and sort of managing it? Right.

Mia (16:11):

And so you could be, you could pick the country that you want to be and you can either win the game by, uh, a diplomacy of victory where you generate enough culture points or you can do the classic way of battling everyone. And so each country in the game, uh, plays on its strengths. Like Germany tends to have their texts that, um, uh, you know, are superior to everyone else. Greece is known for culture and diplomacy, so I like strategy games.

Drew (16:40):

I bet you like to battle everyone, right? Evil genius, <laugh>

Mia (16:45):

<laugh>. I do actually <laugh>, my preferred way of winning is by war.

Drew (16:51):

<laugh>. Oh. I played a similar one, which was like, where you're building, um, like with the castles and sort of like siege, uh, warfare and stuff like empires. Oh, that was fun. That does take me back. They're very addictive, those games cuz it's such a Yeah, there's so many elements to it.

Mia (17:09):

Oh, although I recently got into playing Smash, um, this is like a Pokemon infused with Mario Brothers game, so it's just like battle versus battle. But the, the scenes are really psychedelic.

Drew (17:24):

Well, that sounds like a lot of fun. A lot of fun. Cool. Well, uh, maybe I'll just shoot off my final roundup question. I like to give all of my guests, which is, if you could give your one piece of advice to anyone in the realm of work or career progression, life or self-improvement, anything, what would it be and why?

Mia (17:44):

Uh, I will add a cautionary tale that I, I'm a work in progress. I don't know that anybody should listen to me, but I'll tell you, uh, what I found to be useful because someone told me this. And I learned that instead of reacting to a situation, you should preempt the situation. And I try to do that now and that has helped me grow a lot as a person, um, where I am not just using my emotions to just react to situations and, um, yeah, just helped me become a better person. But I've also tried to apply that in my scientific life, but I also try to prepare myself for the unexpected in general. I feel like that was a really good lesson for me to help me grow where, take a step back, prepare yourself to preempt situations either for discovery or for, uh, something in life. But you don't ever wanna be in a state where you're just reacting to different situations, um, because then you become emotional. You're not in your best mental self to do it.

Drew (18:56):

I like it. That is very strategic and it makes me think of, um, did you know the Art of War by Sun Tzu?

Mia (19:03):

Yeah, I do.

Drew (19:04):

Yeah, it makes me think of that too with like, uh, you know, not being reactive, always trying to preempt what could come your way.

Mia (19:10):

Yep. There you go. That's why I choose battle <laugh> <laugh>.

Drew (19:17):

The, uh, the lab is your battlefield <laugh>.

Mia (19:20):

Exactly. Yeah.

Drew (19:22):

A good note to end on there. Thinking about your strategic moves in life and applying that to any discipline. I'm grateful to Mia for joining me today and telling us all about the inner workings of these sugars. In the show notes, you can find more information about Mia's Research and we'll have links to all the great content from the Scripps Research Magazine to check those out. Thank you all for listening. Hit subscribe and give us a rating if you haven't already, and we'll see you in the next one. Take care.