Epigenetics and DNA methylation

Guest: Dr. Kara Fitzgerald

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Claire Sehinson - [00:00:15]

Hello and welcome to the Fatigue Super Conference today I'm talking to Dr. Kara Fitzgerald about the fascinating topic of methylation.

So Dr. Fitzgerald has completed a postdoctoral training in nutritional biochemistry and laboratory science under the direction of Dr. Richard Lord at Metametrix Laboratory. She's the author and editor of Case Studies in Intuitive and Functional Medicine. She was contributing author to the Laboratory Evaluations for Integrative Functional Medicine (IFM)'s Textbook, and she also co-authored the *Methylation Diet and Lifestyle* e-Book.

She's been published in numerous peer reviewed journals, blogs and podcasts for professionals and consumers. And Dr. Fitzgerald is on the faculty at the Institute for Functional Medicine and maintains her own practice in Sandy Hook, Connecticut.

So welcome to the conference, Dr. Fitzgerald.

Dr. Kara Fitzgerald

Thank you. It's great to be here with you.

Claire Sehinson

Brilliant. And would you be happy first, to share with the audience your own personal experience with chronic fatigue?

Dr. Kara Fitzgerald

You know, I've been talking to Alex about fatigue, you know I've been on your summits and he and I have been in dialogue via email and so forth for years. And it was funny as I was thinking about this conference, I was like, wait a minute, I had chronic fatigue. I had really forgotten about it, which I think for me is like the happy ending, the possibility of, you know, you can, if you're in the middle of chronic fatigue and you're listening to this and clearly many of you are, you can absolutely move through it and get to the other side.

So as I was shaping my questions this time, it was this big, aha, I need to talk about my own journey. And I'm not going to spend, it's tangential but to our topic of epigenetics and methylation today, but it's what brought me to my career really as it does as it has for so much of us, as you were just sharing with me Claire.

I was burning the candle at both ends. Interestingly enough, here's just an interesting sidebar, I was living in a Zen center. I was practicing really rigorous and intense meditation, getting up very early and meditating for hours and then going on to my job. And then I was actually doing my, I was doing, I was preparing for graduate school. So I was doing my studying for my various exams and so forth. And so I

was really burning despite living in a Zen center, living like a pretty monastic life, I was burning the candle at both ends and I wasn't sleeping well and I was getting up very early and so forth.

And doing that for a protracted period I eventually, I crashed. I became really tired and I wasn't able to do anything as the story goes. And so I started to consult with physicians and people, doctors didn't know what to do with me. I mean, I think the most sophisticated thought, they would order standard labs and maybe look at my iron and likely my thyroid was tested, it's going back years now. I was in my mid 20s when this all happened, in later 20s. You know, they just didn't have the panel of labs, it's just like the same story, right, for so many of us.

And one, like one of the most sophisticated docs, I think prescribe me some B vitamins. There's actually prescriptive B vitamins in the state. And I took those and they didn't really do anything. And finally I left the Zen center and I was renting an apartment. And the landlady, this woman who was just in her late 80s and a spitfire, this amazing human being who I loved, loved, loved deeply, she since passed, told me about a naturopathic physician.

And so I went to see a doctor here, he is still in practice in Connecticut, Dr. Jeffrey Klass, and he diagnosed me. So I had, Epstein-Barr was my trigger, sort of like the classic fatigue story. And he turned it around. He turned it around with like some pretty basic lifestyle tweaks. He improved, he emerged me towards a better diet. I was eating vegetarian, but I was eating, I wasn't eating cleanly, anyway it's another story. You think we were eating fabulously in the Zen center and we were kind of.

So he tweaked me towards balance. But he really, he worked on mitochondrial health. He gave me some antimicrobial botanicals. He did a lot of those very basic interventions. And my life changed. My life changed, and I shifted from allopathic school to naturopathic school, like I became aware of that. And here I am today. So that's my fatigue story.

And I want to say too, now that if I burn the candle at both ends, if I push it excessively for a long period, I will flatline into severe fatigue and be in bed or just not be able to lift my arm up. I mean, or just walk or. I can hit severe fatigue states if I push it. But I don't. You know, I'm mindful of that. And so I haven't in years and hence my forgetting that it was chronic fatigue that brought me into this world.

Claire Sehinson - [00:05:22]

Yeah, it's going to be such a familiar story with so many professionals, I think in our industry, a lot of people watching the summit with post-COVID or long-COVID syndrome, that initial viral trigger, but then addressing the whole body, addressing all of the, you know, you might think you're eating the right diet and doing all the meditation in the world, but it could be in the wrong order, it could be in the wrong way. You could be still missing out quite a lot.

Dr. Kara Fitzgerald

I was marathon meditating, it was extraordinary and I wouldn't change that period for the world, but things were a little out of balance.

And one of the neat things about my position was that he walked me towards health slowly, in chunks that I could manage. And it worked.

Claire Sehinson

Yeah. Really overriding that kind of driving tendency or achiever tendency that some of us have.

Brilliant. So, going on to the topic of methylation, because it's a huge area, it's become quite fashionable to talk about in the context of so many types of diseases autism, cancer, cardiovascular disease. I think everything pretty much had a reference to it. Could you give us an overview of what DNA methylation is? And why you find it so important?

Dr. Kara Fitzgerald - [00:06:40]

Sure, absolutely. So I think our world, and you can kind of follow this in practical therapy, in functional medicine when we talk about methylation, we are talking primarily about the methylation cycle, how we're making SAM-e and whether our methylation cycle is up and running. And then from that, we think about methyltransferases, sort of the more classic level transferases reactions like catechol-o-methyltransferase and the some of the other big methyltransferases players, our ability to make dopamine when we're lacking, metabolizing estrogen, that's COMT again, making choline, acetylcholine and so forth.

So we tend to think about the methylation cycle. Is it functioning? Are we making SAM-e? And then we think sort of about biochemical methylation, detox, neurotransmitter synthesis and actually because the methylation cycle sort of interfaces with the sulfuration cycle we think about, we tend to think about those two, cysteine, glutathione, etc.

So that's where our, as conditions I think our brains grow quite a bit. At least with mine, that's where my brain went, looking at homocysteine, looking at other, looking at SNPs associated with methylation and inferring glutathione started.

And we do that in the lab, we've been doing that in the laboratory during my post-doctorate training as well. So epigenetic lead up for me, I started to look at it a little bit, probably in, you know, it's been around for a little while. It's a new science. I mean, it's kind of spring boarded into prominence after we mapped out the genome. So that was about early 2000, 2003 or so, we mapped the genome out. And this idea that we were going to find one genetic mutation relating to one disease was shot. It was just this kind of extraordinary moment in science when we thought that we were going to really understand disease physiology in this very direct way. And instead, it just blasted us into this transformative omics era where we started to look at the epigenome and the [inaudible], all of these products of DNA activity.

So I don't want to get too crazy complex here, but with the mapping of the genome and sort of realizing that it was infinitely more complex than what we anticipated, we started to look at the epigenome. And research turned, the volume of research turned way up at that time for epigenetics, and it's been galloping forward since. But there was a real dearth of research prior to that.

And in fact, let me tell you, we've been doing a research study and our scientific adviser, Dr. Moshe Szyf is a premiere, you know one of the first epigeneticists in the world, he's up at McGill University. He started the journal epigenetics to just kind of give context.

He was aware of DNA methylation back in the 80s. In fact, they were looking at the lab he was at the time in Israel. And it was sort of considered junk, like it wasn't relevant, you know, sort of like what? Like sometimes we term junk DNA, people might have heard of that. Now we know that that so-called junk DNA actually regulates. But same with DNA methylation where the methyl group, that's the carbon and three hydrogens, sit on certain specific regions of the DNA. Back in the day that was really considered to be, just irrelevant sort of debris to be scraped, to to be ignored.

It was his lab, actually, that said, that identified not only was it not to be ignored, but it actually, that it played the fundamental role in regulating gene expression. And so it was his work, but and a lot of other scientists, who really began to crack open the nut that said epigenetics is a big deal.

And there are a number of different ways that we control, that the epigenetic landscape controls gene expression. But DNA methylation, these methyl groups on regions of the DNA, that when there are a lot of methyl groups, it tends to turn off that gene. And when there are few methyl groups that gene is on.

That's certainly the best studied of all of the epigenetic marks. And it seems to be the big player. I say that, you know, more science is to come, it's just this massive field.

So going back to my evolution, being as interested in methylation as I was and am, I had to put some energy into thinking about DNA methylation in all the interventions that I'm prescribing to my patients

on a daily basis, the B12, the folate, etc, betaine, am I influencing DNA methylation? Am I doing so favorably?

[00:11:51]

And as I unpacked that research, I was really kind of stopped in my tracks because the bulk of the early science is in cancer. And in fact the bulk of the science and epigenetics continues to be in cancer and the tumor microenvironment is extraordinarily efficient at highjacking epigenetic expression for its own propagation. So the tumor microenvironment will use DNA methylation to turn off tumor suppressor genes like our good genes that we want on. It will use the DNA, it'll demethylate regions of the genes to turn on oncogenes and allow for its propagation.

So that first body of research really stopped me in my tracks in that there are unhealthy patterns of hyper and hypomethylation and therefore we need to be more nuanced in how we prescribe methyl donors. Like you probably, in the most extreme example, for somebody with active cancer, unless you have a good reason, like a profound anemia, macrocytic anemia, you probably want to be mindful about loading them up on methyl donors.

It brought to me a more nuanced thinking with regard to methylation. And the other piece that I want to say, that I got very interested in, was the whole role of biological aging and how it seems to, it's trackable through DNA methylation and probably our aging journey, well, we can say that our aging journey is closely influenced by our DNA methylation patterns. And when you drill down onto that a little bit further, you'll see that all of the chronic diseases associated with aging, aging is the biggest risk factor for chronic diseases of all types, you'll see this disordered methylation patterns.

So, almost like the same kind of imbalance I've just described in cancer. You can see the different flavors of it in cardiovascular disease, in diabetes, in chronic fatigue. You can see it in depression. You can see it in different stripes of depression, like postpartum depression disorder or what else, in autoimmune disease and on and on.

And, so we developed in our practice, back in early 2015, a methylation, diet and lifestyle program. Rather than just pushing methylation forward aggressively with B vitamins and so forth, what if we go way upstream and influence it with diet?

Additionally, it turns out, not surprising, that there are habits like balanced meditation, maybe not quite what I was doing back in my 20s, but or an exercise, getting adequate sleep. Like a lot of the important components of health that we're leaning on now in our practices in functional medicine have favorable influence on epigenetic expression.

We also discovered this whole line of nutrients that seem to have, so methyl donors are going to help make methyl groups which when on DNA inhibit DNA expression and its essential. In fact, as we age we tend to methylate less efficiently. But then there are these regions of hypermethylation. So globally, aging is a hypomethylation journey with regions of hyper.

And so even though we, so we need to bathe ourselves in lots of methyl donors, I think ideally through food. But then we want these regulator nutrients that go in and support sort of balance. It seems like they may influence putting a methyl group down in the gene in the right location. So you've got a big green salad and then you throw some blueberries and rosemary and maybe a little bit of turmeric in there or whatever, use a turmeric dressing, and that is a folate, that's a methyl donor rich meal with these sort of methylation adaptogens, these polyphenols that help position it.

Claire Sehinson

I think that's quite an interesting question. I think one question that would always come up with the methylation of DNA, where you've got hyper and hypo methylation states, and seemingly the body knows what to do, when to methylate at what time of life, because certain patterns change over a lifetime.

But when you sort of take excessive methyl donors in supplement form, you kind of think, where does it go? How does it know where to go and what part the gene? I guess the diet and lifestyle it's gentle, but all of those phytochemicals that come with methyl donors in the foods are telling the methyl groups, if you like, for lack of a better explanation, where to methylate on genome. Is that how it works?

Dr. Kara Fitzgerald - [00:17:02]

Well, it seems that way. I mean, obviously, we need to be drilling down into the science here. First of all, my apologies for that massive dump. I hope people track with me and Claire whatever you need to tease out, go back and do it. But, yes, it's so interesting how there are phases of methylation, of DNA methylation through the life and preconception, conception, early childhood. All of them are important for different reasons. So I just, I want to underscore that.

But it does seem to me that, yes, this combination might regulate how we methylate and support us to methylate favorably. In our research study we did show that, with regard to biological aging. So we did show that because our participants actually got younger as measured through DNA methylation the Horvath biological age clock, it's like they repositioned where those methyl groups are on their DNA.

So we didn't have this net increase in DNA methylation on their epigenome, but we had a repositioning. I mean, that's...

Claire Sehinson

That's huge.

Dr. Kara Fitzgerald

And it was a favorable repositioning. I know, isn't that cool?

Claire Sehinson

It's crazy.

Dr. Kara Fitzgerald

It's like so cool.

Claire Sehinson

I mean, would you be happy to go, just recap the study for anyone who doesn't know it? We can link it also in the conference notes.

Dr. Kara Fitzgerald

It's just about, we were accepted in the Journal Aging, which I think is the best home for it. And it's not out yet, but just stay tuned, and it's an open access journal so you can get the full text. And yeah, as soon as it is, we'll pop it into your show notes.

So basically, we took the methylation diet and lifestyle program that we developed here in the clinic and we prescribed it. It's a controlled trial, a pilot controlled trial. So 18 men and 20 control middle aged men. And the only reason we didn't do women, I'm so sorry we will, we will, we're doing a larger study, is just because we wanted to look at middle aged when methylation starts to really change. And we would have dealt with women in various stages of menopause. So premenopause, peri and then post and that would have been hard with such a small population. So we started with men.

And so our control group they were not prescribed anything. And then our intervention group did the diet program. They did it, had an exercise prescription, we tracked their sleep and they did a twice daily brief relaxation response program. Our nutrition team here, we lean, as you know, very heavily on nutrition. And we've got a really great program headed by Romilly Hodges, who was a Brit. And just, actually she's been in Zurich, but she's going to head back here soon in the States, but she's been managing our program from afar. We had a coaching team, so a nutrition trained coaching team that worked with our participants.

And incidentally, let me just say, that we analyzed adherence to the program and it was very high. So just giving the shout out not only to our participants, but to, I think the nutritionists working with them was really important. So they did that, they followed the study program for 8 weeks and then we did a baseline, mid and end, we got a massive epigenetic test done as well as blood tests.

The epigenetic test is available in research setting only. It's from a research lab called Alumina, and it looked at almost a million of these methylation sites on DNA. And we looked at other types of methylation as well. So at the very end of the study, we found that their triglycerides dropped considerably.

What else did we do? We increased their folate. So no supplemental folate, but we increased, we were able to increase their circulating methyl folate. What else? Cholesterol dropped. There's a tendency towards less anxiety. These were very healthy guys, though, so we didn't, we weren't looking to tweak those things because they started out at baseline healthy. And then, of course, really our most stellar finding right now is just that we were able to reverse biological age as compared to the control group by over 3 years.

Claire Sehinson - [00:21:32]

Wow. And in 8 weeks, which is incredible.

Dr. Kara Fitzgerald

In 8 weeks, yeah, yeah, that's right. It's the first of its kind study. There are, there's one other year long study using a Mediterranean diet and in that group most of the people did not experience any reversal of biological age. A subgroup of Polish women, it was a study conducted on Italians and Poles, and subgroup of Polish women seemed to have some reversal. But it was over the course of a year.

Claire Sehinson

Wow. Yeah, that's incredible. I can't wait to see that study. It's so much for the diet and lifestyle side point of view without supplements and yeah, it's exciting to see what happens there.

Dr. Kara Fitzgerald

We did a probiotic, we did use probiotic and greens concentrate, a polyphenol concentrate. Those were only two so-called supplements. But no methyl donors.

We are writing it up for publication. So not only a research study, but we're writing it up in a book for regular people and we have an app coming out. So in our show notes, just if you can sign up for the newsletter and you'll just be able, you'll have access to all of this, you'll be guided towards if you're interested in doing the program, how you can jump onto it.

Claire Sehinson

Yeah, and there's so many applications for the methylation diet and lifestyle as well for all types of conditions. Even if you're working with complex infections or toxicity, that's kind of a foundation for a lot of people. And because it's diet, it's really safe. There's no danger of over supplementing, which we see a lot of people do, self supplement or practitioners based on tests.

And speaking of tests, what kind of laboratory assessments do you like to use in practice?

Dr. Kara Fitzgerald - [00:23:14]

Let me just, let me say just one other thing about what we're working on. I'm developing an epigenetic test, so it won't be the crazy almost a million CpG sites or methylation sites that we used in ours, but it'll be, I'm going to choose about ten thousand, which is still a ton.

Claire Sehinson

That's a lot.

Dr. Kara Fitzgerald

I know it is. So if you get it, you'll have biological age, as we did in our study. I'm also going to be looking at some of the things that I'm really interested in, like suppressing, cancer or tumor suppressor gene methylation or oxytocin or what else? We'll be looking at genes associated with obesity and type two diabetes and we'll be looking at how they change over time with our intervention. So there's pretty cool, exciting stuff around. That's not available in our practice yet.

So in my practice, I do a lot of standard chemistries. I do a broad nutrition body of tests. I look at, just coming from a functional specialty lab where I did my postdoc training. I'm comfortable getting those kinds of labs, so organic acids and amino acids and fatty acids. I do some genetic testing. I don't do as much as I used to. What else do I do? I do breath test. I do a lot of stool testing. I do, I like looking at hormone panels and I like looking at how hormones are metabolized. And so we do quite a bit of that here as well.

Claire Sehinson

Ok, so just a broad range, I guess what the individual needs.

In terms of genetics and epigenetics, do you tend, do you use, because a lot of people order, and they can now just on the internet order things like 23andMe panels and they get this huge plethora of data, a million SNPs, and then they're not quite sure what to do with that. Do you get clients like that? And then do you encourage them to do metabolomics with it to make it more clinically relevant?

Dr. Kara Fitzgerald

Yes, exactly Claire. That's exactly right. So one of the reasons we even developed the methylation diet and lifestyle is because we thought we were, myself included but others in my field, were sort of overstating single nucleotide polymorphisms and treating pretty aggressively. I mean, I think I've always looked at biomarkers but some people stop at SNPs. Oh, you've got SNPs, that's Y and Z, you need, you know, a lot of vitamins, A, B and C. And I don't think that's fair for many reasons.

And you're absolutely correct. You want to see is there evidence that this gene is not functioning? Is there biochemical evidence that we can put our fingers on that will suggest we need to treat? And I would say more often than not, the answer is not.

You know, I wrote about this actually in my book. I mean, when we first had access, in the lab we were doing organic acids and amino acids. We were looking at the metabolin, as it were, the early metabolin. So we were looking at the products of gene expression and antiemetic activity. And I thought, wow, now that we have all this SNP data, I'm going to layer it in and I'm going to see this really clear story. Right. If you've got a SNP and catechol-o-methyltransferase probably have like, you know, you don't metabolize your adrenalin at all and therefore you're very anxious.

Well, you know, some of the time that's true. Right. A subset of folks might have that, but a lot of people don't. So, you know, as I would look at SNPs and expect to see it in my patients data or clinically, I was disappointed. I want to layer in though, that those enzymes or those SNPs that were so

enamored of can be changed epigenetically. Their expression can be changed epigenetically and you won't pick that up on a 23andMe.

So you can have an MTHFR subfunctional because it's hyper methylated. And you won't see that you need to look at homocysteine or you need to look at whether some of the products of that enzyme.

Claire Sehinson - [00:27:36]

So measuring the end products is actually more clinically relevant.

So I guess going into some of the genetic testing that some people do around things like breast cancer, the BRCA gene, that's an area, that's quite a hot area if you have this gene a lot of people become quite fearful.

Dr. Kara Fitzgerald

Let me just say...

Claire Sehinson

Sort of thinking mentality.

Dr. Kara Fitzgerald

If you, yeah. Is 23andMe doing any kind of BRCA work up these days?

Claire Sehinson

I don't know. No, I don't know.

Dr. Kara Fitzgerald

There are hundreds of potential variants on the BRCA. BRCA is a massive protein, there's BRCA1 and BRCA2, it's massive. So there are literally hundreds of different mutations. And you need to, if you get your BRCA mutations tested, absolutely, unequivocally, have to work with a genetic expert who can kind of stratify your risk because some of them are no risk at all. Some of them may be slight risk. Some of them, of course, high association with cancer.

But let me also say that back when we first characterized the BRCA mutation, actually, let me restate this, so the original scientists to characterize BRCA looked over time, and saw that from the 40s, so they were able to access and analyze blood from the 40s and going forward, and they saw the incidence of BRCA associated cancer has increased exponentially with time.

And what that means is more influential, it's not the mutation as much as it is our lifestyle. So a mutation doesn't increase rapidly, like over 50 years or 60 years or so. You wouldn't see that influence, it is environmental. So even when you have a BRCA mutation that's significant, you need to get in there with the environmental work, you know, lifestyle work and so forth.

For anyone who has a BRCA mutation, in fact, it can influence the way that we're making estrogen and metabolizing it and so I would obviously pay careful attention there. But the take home is that there are many BRCA mutations and you absolutely have to make sure that you talk to somebody who's very qualified and versed in it.

Incidentally, BRCA can also be methylated. So you can have, and it's influential in cancer, so you could have a, basically a BRCA protein acting like it's mutated, even though it's completely functional if you measure the gene itself because it's methylated. And that's an area of investigation that's kind of cooking up now. And we'll be looking at, we'll actually be looking at methylation status on the BRCA

protein in our customer array that's forthcoming. So super interesting. And the take home, as you say, is that it's not an all or nothing journey by a long shot.

Claire Sehinson - [00:30:43]

Yeah. And there's so much environmental influence, which is important to assess and to see what the drains on the methylation donors are, to see what additional load the body is dealing with. So I guess that's something you probably assess as well in clinic, the environment toxicity.

Dr. Kara Fitzgerald

Yes, absolutely. Unequivocally. Yes, yes, yes.

Claire Sehinson

Yeah. And and I guess it goes back to, you were talking about the whole genome and how, I think it's the majority of it, is something like over 90 percent, isn't it? They used to call it junk or non-functional, but it's actually regulatory, the methylation patterns are really important.

But I think the other thing to note is cancer is really poly-genomic, isn't it? So it's the balance of the things like the p53 and then the other sort of genes.

Dr. Kara Fitzgerald

Yes it's complex. There's a lot going on. That's right. That's right.

Claire Sehinson

It's not just BRCA, yeah, it's multiple genes interacting.

Dr. Kara Fitzgerald

That's right. One of the fascinating discoveries in our research was that glutathione S-transferases. A lot of you listening know glutathione and love glutathione and you know, it's our master energy oxidant.

Well, it turns out that one of the glutathione enzymes can be hyper methylated. So, one of the glutathione enzymes, the glutathione S-transferases, actually not, some of the other glutathione enzymes are considered tumor suppressor genes because their ability to detox is so wildly important to preventing cancer that they have the label of tumor suppressor genes, and so they can be hyper methylated in cancer. Cancer will shut down our ability to detox them, shut down access to glutathione and specifically, like in genital, urinary cancers they've looked at this.

What does that mean? I don't want to send people off with a whole lot of anxiety. This means that we want to get in there aggressively with a diet and lifestyle program and we want to think about toxin exposures and these polyphenols, these so-called methylation adaptogens have been shown in vitro to allow for the re-expression of these formerly hyper methylated and inhibited genes. So this should be, hopefully, something empowering and positive. There's a lot you can do to optimize that.

Claire Sehinson

Yeah, absolutely. I think another of the genes that had a lot of attention, I think, in cancers was GSTM1 which I think affects over 50 percent of the population that actually are missing that gene completely. So I guess knowing that information, you can look at it in a very scary way as in with your BRCA status or you could go that's a real opportunity to intervene. So I think that's what we're trying to highlight with this sort of testing, is that it's real, and I doubt you'd put anything out that isn't modifiable it's all clinically relevant, there's something you can do about it. So that's hugely empowering.

Dr. Kara Fitzgerald - [00:33:39]

And even, you know, back in the lab, we saw that the most entrenched genetic conditions, there is a condition called Melnick-Needles syndrome. And it's a bone and collagen disorder. It's diagnosed at birth and it's severely debilitating. It's X linked and so it's in males. And they generally don't, boys don't survive with it. Your life expectancy is very, very young. So this is a severe, impactful genetic condition that we made a massive difference. The boy that we worked with, the last I checked in on, he was graduating high school so he's no longer a boy. He's the oldest living individual with Melnick-Needles.

It's because his nutrition program was completely designed on the laboratory testing. So his nutrients were just in exquisite alignment with what his body needed.

It was yeah, it was amazing. He required a feeding tube. And so his nutrition interventions were just very impactful. We've seen this in Down Syndrome, you know another condition we don't think that we can influence, right, it's just this potent genetic condition. And in fact optimizing nutrition absolutely helps it. So even when you think that there's no hope, there's big hope.

Claire Sehinson

Yeah, amazing. I mean, yeah. Even with a Darwinian type mutations, which are the minority of illnesses, it's amazing to know that you can actually make a difference.

Dr. Kara Fitzgerald

Yes, that's right. Because if you think of the body as a web, you know, like all sort of, any influence, any favorable, so inflammation or the diet is going to just augment sugar or insulin, it's a web on the entire being, it's been pushed down the entire being. And conversely, optimal nutrition having enough of a broad spectrum of nutrients and good lifestyle habits is going to like free that web up and allow it to function. So even when you have the weight of a significant genetic mutation, we can still optimize function.

Claire Sehinson

Yeah, yeah, absolutely. And there's ways around that path way, a bit like neurology, you know, one pathway is not functional, but you can adapt different coping mechanisms.

Dr. Kara Fitzgerald

Well, going back to your glutathione, your comment and the fact that many of us are, glutathione enzymes are incredibly redundant, aren't they?

So, yeah, you may have glutathione S-transferases p1, I think that's what you said, right? But there are other glutathione enzymes and just a fabulous redundancy. So I think in the most important biological systems, we've got some redundancy.

You know, thinking about the COMT mutation and metabolizing adrenaline, there's other ways to get adrenaline out of the body. So, yeah, I think we, our body planned, physiology, evolution sort of planned..

Claire Sehinson

Had a backup plan.

Yeah. So another really interesting area that I want to speak on was the biologically embedded experience. Could you define what that is? I know there's some really interesting research in terms of stress, yeah.

Dr. Kara Fitzgerald - [00:37:05]

Yeah, yeah, yeah. You and I were talking about the heritability of epigenetics. So, you know, again, we think heritability is limited to genetics and therefore it's going to take millennia before we see any favorable influence. But it turns out that epigenetic changes are heritable.

And just going back, you and I were talking a little bit in the beginning of our conversation around different life stages. Well, in embryogenesis, when sperm and an egg are growing to create a new being, it turns out that most of our methylation marks that, mom and dad's DNA are packed with their various methylation patterns. And then when they come together, most of those are actually wiped clean in the new fetus, and then new marks are laid down. But a portion of them, about 30 percent remain. And that's the heritable stuff.

And it's pretty extraordinary. And it can go way back. We have not tapped the extent of epigenetic inheritance. But we do know, as you were pointing out, from like the Dutch Hunger Winter, you can just Google Dutch Hunger Winter and pull up those studies or pull up the Wikipedia entry for an easy read on it, and see that generation zero, so experienced in the case of Dutch Hunger Winter, Germany withheld food from a region in the Netherlands and they starved for a discrete period of time during World War II.

And women who were pregnant during that time, particularly early on in the first trimester, gave birth to offspring who had epigenetic patterns that prompted almost like, what we call a thrifty epigenotype. So they hung on to every calorie they had. They gained weight more readily. Their cardiovascular disease was up, diabetes was up, actually schizophrenia and so forth also. And we see that they've past that into subsequent generations, some of these epigenetic changes.

Likewise, we've seen the stress, the psychological and physical stress influence being passed through the generations. And there's something Dr. Moshe Szyf again at McGill, was working on, called Project Ice Storm, where they looked at a single two week ice storm event in Montreal and the surrounding areas. And women who were pregnant at that time gave birth to offspring who had higher rates of autism and asthma.

And what else do I want to say about it? We see stress disorder, total life stress, post-traumatic stress. We see that biological embedding of those experiences onto the epigenome. And we see that heritable also. And you know what? Most of the research is focused on the negative. And we need to be looking at post-traumatic growth, as you guys talk about, which is so important and resilience. And what do those patterns look like?

There's one, maybe two papers to my mind that actually look at that. And so some people can sort of rise from the ashes, like people working at your clinic, for instance, like this phoenix rising from the ashes. You know, they develop this resilience and that shows up in biological embedding too. And you can actually pass that down. I mean, it's just an exciting and extraordinary area that I just, I'm obviously inspired by.

Claire Sehinson

Yeah, it's amazing. I mean, in terms of things like PTSD, which you think some people get that, but other people really grow from that. Do you know what genes are...

Dr. Kara Fitzgerald

Let me actually, let me actually kind of circle back. So I have a podcast with Dr. Moshe Szyf, if you want to hear him talk about this. So interesting. But his vision is that we actually test mothers and we look at their epigenome, you know, that we look early on and we figure out, we identify those patterns that are in disarray. And he's already started to do some of that research. And we know some of the vulnerable genes. I can talk about those in a minute. And we look and see what we can tweak and then do it. And we use methyl donors, so this would be an appropriate time for an intervention of B12 or folate, as indicated, to favorably shift back that epigenome after that traumatic event.

And then, of course, using the diet and lifestyle interventions would also make a difference. And we know that from the literature. So meditation and exercise and adequate sleep, all of those are major players, as powerful as the diet is on epigenetic expression. So we could create an intervention that would favorably influence not just mom but offspring and dad is in this as well, we inherit our father's epigenetic patterns too.

Claire Sehinson - [00:42:10]

Yeah. And which genes were you, did you find or did Dr. Moshe find relevant to kind of the post-traumatic stress disorder phenotype? Or the post-traumatic growth?

Dr. Kara Fitzgerald

You know, one of the genes that he's looked at, he's done a lot of research in this arena in a lot of the earliest animal studies. And so, he's looked at the glucocorticoid receptor and also the arginine vasorpressin gene, which helps regulate glucocorticoid. So some of the clear genes that you would associate with imbalanced stress response, we can see those either on, accessibly activated or hyper methylated and turned off.

One of his famous studies, and this has been repeated in humans and demonstrated in humans as well, is when mice were not sufficiently, baby mice were not sufficiently groomed, basically cuddled early when they were first born. Their epigenetic, so their stress response was heightened, meaning that they would get stressed out more readily. So when they weren't adequately nurtured by their moms, their stress, their epigenetics shifted towards a ready stress threshold.

Conversely, when they were nurtured, actually it doesn't even have to be their moms, which is interesting. It's just when they were adequately nurtured by a care provider, their stress threshold was resilient and normal versus a lack of that. And I think that that's important, particularly for me as an adoptive parent, that it doesn't require a biological connection.

Claire Sehinson

That's hugely important, actually, because I think people sort of think, a lot of people who adopt, and their children might have been offspring of, I guess, substance misuses, I'm thinking of a particular person I know as she worries that child's kind of been set up for a negative health outcomes later in life. But actually, I think she's doing all of the right things in promoting cuddles and oxytocin and all of this lovely, nurturing molecules. And that is reprogramming this child's epigenome.

Dr. Kara Fitzgerald

Yeah. In fact, doxazosin receptor is another gene that we can see methylated or on or off in different stress conditions and also heritable. But yeah, that's exactly right. That's exactly right.

So yeah, this child came into the world with probably some lousy epigenetics from, you know, inherited from the biological mom and perhaps the father as well. But we can re-program them.

You know, every time the cell divides that's an opportunity for that DNA methylation pattern to be laid back down or actually changed. And, you know, it's extraordinary when we look at the literature at how rapidly things can change. So things can become very resilient and heritable, but things can turn around fast.

There was an interesting study on pollution that showed just 4 hour exposure to, not excessive pollution, you know, being in the city, changed epigenetic activity in 4 hours, just rapidly altered it. So there's a continuum of the durability of those marks, but certainly over time with lots of cuddles, just like, yeah, I mean, I think we really can move things around.

Claire Sehinson - [00:45:50]

Yeah, absolutely. And I guess the turnover, does that depend on how fast the cell divides? So there's some tissues which rapidly divide and others like the brain which technically don't undergo mitosis, does that make a difference?

Dr. Kara Fitzgerald

So that's a really good question. We've seen methylation changes in the central nervous system. And so, I had this conversation with Dr. Szyf actually and, you know, is it contingent on cell division? And he said no. And he would be focused more specifically in the central nervous system. And we don't I mean, we do, we see it.

So the other way. So there's methylation changes with cell division. And that's in such a perceptive question. But there's also what we call active demethylation, and that's happening. So this would be methylation changes outside of cell division. And that's happening all of the time. And we can support active demethylation and we see that in the central nervous system. We see this active demethylation and there's actually a few different steps. So there's these methylation intermediates that are produced that they look at in the central nervous system. They look at it in the total physiology, but specifically in the central nervous system. It seems to be a big deal. And that certainly could be influenced by the slower rates of cell turnover, if at all.

Claire Sehinson

Yeah, yeah. That is really, really interesting.

Dr. Kara Fitzgerald

Going back to the methylation diet and lifestyle there are nutrients that help this active demethylation. So these enzymes are called Ten-eleven translocation enzymes. They are, vitamin C is involved there, vitamin A, vitamin D, Alpha-ketoglutarate which is a nutrient in the mitochondria, is a co-factor. Even iron, so if you're iron deficient you're going to influence active demethylation.

Active demethylation helps clean things up. So we want it functioning. And so we built it when we were designing our diet. We were also thinking about active.

Claire Sehinson

Oh, fantastic, I guess how do other chemicals like brain-derived neurotrophic factor or other neuropeptides interact with all of that?

Dr. Kara Fitzgerald

You know, it's the same. It's sort of the same story, it's pretty crazy. You can see it in Alzheimer's disease, even early mild cognitive impairment. You can see [inaudible] hyper methylated and inhibited. We also know that we can turn it on through exercise. So same kinds of things are going to be important there. Again, the glucocorticoid receptor can be hyper methylated and inhibited or inappropriately expressed.

And we see that actually, we can see that sort of Venn diagram overlap in cardiovascular disease and cognitive impairment with the glucocorticoid receptor methylation change. So the stress response in forming these really ubiquitous diseases, you can see in DNA methylation patterns.

Claire Sehinson

Hmm. I mean, I guess a simpler question is, what is the impact of stress on methylation? Is it again really complex?

Dr. Kara Fitzgerald - [00:49:19]

Well, just going back to the Moshe Szyf research, you know, and seeing and also in humans the massive change to our ability, our resiliency to stress based on early childhood influences. So there's, so we know that there's that, post-traumatic stress disorder can have a powerful influence on DNA methylation, total life stress can have a powerful influence.

We also know that the biological clock that we looked at in our study, up to 25 percent of those genes are influenced by glucocorticoid activity. So the stress response plays a role in biological aging as well. So I would say of all, honestly, stress informs everything, stress is a big deal. Like our ability to work with it, it's life, it's part of life, the stressed experience. But how we manage it and giving it the attention that it deserves to sort of turn the volume down and not allow it to take us over like it did for me when I was in my 20s, is hugely influential in our ability to turn the volume on these diseases.

And if we're preconceptions, or if we're family planning, you know, in what we're going to pass on to our offspring, epigenome of resilience and the ability to handle stress well or a reactive type.

Claire Sehinson

Yeah. And I guess going back to things like the Dutch Hunger Winter, and I'm not sure if Ice Storm tracked this, too, but they looked at different stages in pregnancy and different health outcomes that would happen. Can you speak on any of that?

Dr. Kara Fitzgerald

I mean, I know that that first trimester tends to be, is the most impactful with regard to changes to DNA methylation. Because that's when cells are, so stem cells, we've got the pluripotent stem cells and their fate, their phenotype, is defined by methylation. And that's active really early on. And this is one of the reasons why folate like, you need a methyl donor rich diet during those times.

But we also want, I think, all of those other nourishing methylation adaptations. And the Ten-eleven translocation enzymes are also big players. Those demethylation, those active demethylation, TET enzymes as they're called, are scrubbing the DNA clean in the offspring, in the embryo from mom and dad. And then the new marks are being laid down via DNA methyltransferases enzymes. So there's a family of both of those that are in there doing their busy work. And then the stem cells fate, the phenotypic fate is decided.

In fact, in females one of our X chromosomes is methylated and inhibited in each of our cells. So methylation I mean, it's just a big deal. It's a huge deal in genetic expression.

Claire Sehinson

And I guess that affects every cell of our body in every stage of our life.

I mean, just going back to stem cells, also, you talked about cancer, tumor cells being very similar characteristically to stem cells as in they're really monoclonal.

Dr. Kara Fitzgerald

As we age.

Claire Sehinson

As we age.

Dr. Kara Fitzgerald

Well, you know what's crazy? Oh, my gosh, I hope people are tracking with us. But so as we age, stem cells are, we talk about stem cell exhaustion that's a term that's batted around our world all the time.

And the vision is, is that we're not making stem cells and we need to make more stem cells. In fact, as we age, we're actually making loads of stem cells. We're still making, we're making even more than we used to.

But they're not being defined. They're sort of, they're stuck in this pre-definition state, the stem cell state. So they are, there's like monoclonal expansion and they're not going on to become actually, I'm specifically speaking about hematopoietic stem cells, so they're going to go on to be white blood cells, red blood cells and so forth, but they're not. And that's one of the reasons why you're going to see a drop as we age in our immune system, this fundamental piece here.

Why is that happening? Well, it turns out that DNA and methyltransferase three, so DNA methylation again, decides the fate of stem cells. And in a stem cell microenvironment, you can see some of the same inflammatory components that we do in cancer and I think in other chronic diseases where methylation becomes disordered.

So, again, focusing on optimizing DNA methylation will help us here. I think, you have to do research in this arena, but I think optimizing DNA methylation with a broad program will just help stem cells kind of continue and remain, go on to be defined and make sure the cells, etc. Yeah specialize, right.

What did I want to say about this also? So, yeah. So in this monoclonal state, this undifferentiated state, cancers are at risk, like the leukemias and so forth.

Claire Sehinson - [00:54:51]

Yeah. So they're rapidly kind of, mitosis.

Dr. Kara Fitzgerald

Dividing.

Claire Sehinson

Dividing, that's the word. And just really unspecialized. So not really performing the functions of the tissue itself. And I guess you see a whole host of immune disorders and that sort of thing.

Dr. Kara Fitzgerald

Yeah. And two big players are DNA methyltransferase enzymes, as well as the Ten-eleven translocation enzymes. So that little package we've been talking about the enzymatic dynamic duo that we've been talking about in all of these conditions is right there as well.

Claire Sehinson

Brilliant. Off the cuff, but what do you think of people who harvest their stem cells? I think you can harvest pluripotent stem cells from the wisdom teeth and people are banking that. Is that...

Dr. Kara Fitzgerald

If you actually want to have I mean, you know, the idea that they're pluripotent, the only time they're pluripotent, so they're undifferent, they're that far, is in embryogenesis I think. That's when they're truly pluripotent. Otherwise, their fate has already been sufficiently decided. At least that's my understanding. If anybody wants to, has evidence that I'm totally bonkers then maybe send me a paper showing me otherwise, what do I think?

Well, you know what? My mom is about to do some stem cell therapy for her really severe osteoporosis and excuse me, not osteoporosis, osteoarthritis in her knees. And I'm really excited about it. But, and as her physician here advised and I'm in complete agreement with it, she needs to

be eating super cleanly like her body, for her to get the most ben from those stem cells, she needs to have her nutrition status really dialed in.

And fortunately, she gets it and she's doing a really good job with that. And that's when we're going to be able to have some vigorous stem cells. So, yeah, I think harvesting stem cells, if they're viable and they can stay viable over time, harvesting them when we're young and maybe and using them when we're older, or in my mom's case, just living our best life and harvesting them when she's as healthy as possible and using them, she's going to be doing this in a couple of weeks. Yeah, I think there's absolute place for that.

Claire Sehinson - [00:57:09]

I know it's sort of in quite far progressed infectious diseases and it's been utilized, but I guess the main point is you still need the methylation, they still need to be methylated in order to turn into specialized cells that actually function. So, yeah, the diet and lifestyle goes hand in hand with all of that.

So with, you know, we've seen the kind of long term benefits of a methylation diet and lifestyle. It's more sustainable and you're allowing the body to do the right thing at the right time, with the wisdom it has. When is supplementation appropriate? So the context here is, some people, the quality of our food these days perhaps is not as nutrient dense, the processing, inflammatory bowel conditions, absorption. What do you?

Dr. Kara Fitzgerald

Yeah, well, I think we know how to define that, right. We know, if somebody got necrocytosis, you know, they're going to require some aggressive B supplements. I would say, and maybe not aggressive, but you need to get in there and correct the macrocytosis or macrocytic anemia or during pregnancy. You know, women may need a little extra help with folate and B12. I would pay attention to it, make sure they're getting adequate nutrients in their diet, of course. And I would also be mindful of not consuming folic acid containing foods, so food fortified. Does the U.K do fortification?

Claire Sehinson

Yeah, yeah. Bread and cereals.

Dr. Kara Fitzgerald

OK, so I would avoid that and I would go with natural bioactive folates. But I think sometimes supplementation is needed, actually fairly regularly supplementation is needed. If there's a significant malabsorption issue, yeah, if there's just evidence biochemically or clinically to do supplementation, I think it's OK.

I would have an endpoint in mind. I would get away with the lowest possible dose. I would be very careful in conditions like cancer where you might be actually pushing things forward. And there is a u-curve, so we know that, let me state this because it's super important. So methyl donor deficiency can promote cancer that's been very well documented. And methyl donor excess it looks like can as well. And there's some large studies, in fact, there's a study called the B-PROOF study where they were looking at B12 and folate to prevent fractures in osteoporotic older people with high homocysteine. So they were correcting homocysteine and then they were looking to see if that prevented fractures.

The only difference it made were in the very oldest. So 80, I think, and above actually had some benefit. But what they did notice is a significant increase in the incidence of colorectal cancers. And they reanalyzed it a couple of times because people were surprised with that finding. And that's not the only study that suggests that. So think about these nutrients in u-curve. Deficiency is a problem and you want to correct it. And excess in certain conditions can be a problem. So you want to get in

that sweet spot. So supplementation can be appropriate, but maybe have endpoints in mind around it. And transition over to food.

And let me actually just say that there is no research at all showing food, sort of dense methyl donor diet itself as being problematic. And in fact, there is research out there showing that it's protected. So you don't have to worry about sort of bingeing on your arugula and your kale. You're not getting too much folate.

Claire Sehinson - [01:00:59]

Yeah, exactly. And I guess the body knows how to regulate that and kind of excrete anything that's an excess in food form so it's generally much safer.

Ok, perfect. Being really conscious of time because we could talk about school all day long. But if people want to find out more about you and your work and the methylation diet and lifestyle, and obviously your study, how can they do this?

Dr. Kara Fitzgerald

You can start by just going to the website, just my name drkarafitzgerald.com sign up for the newsletter. That's going to be your best bet. You'll see that we're going to be launching a page where we're going to be capturing emails for people who want to hop into our beta study with the app and the program. So people who want to get right in there at the beginning and have access to the test as soon as it's out. It's going to be just a small population at start. But as we move through that beta testing it'll get larger and bigger and it'll be a lot of fun.

So I think the easiest way to do that is to just get over there and sign up for my newsletter. But anything that comes forward I'll shoot your way so that you can add to your show notes.

Claire Sehinson

Perfect. Thank you, Kara, so much for the conversation today.

Dr. Kara Fitzgerald

Thanks.