What's Work Got To Do With Epigenetics?

Guest: Dr. Mitch Turker, Ph.D., J.D.
Host: Sam Greenspan, M.P.H.

Helen Schuckers: 00:01 You're listening to What's Work Got to do With It, your go to resource on all things workplace, safety, health, and wellbeing. You've probably heard many times that work, diet, sleep, and stress can impact your health, but do you know how and why? We went to one of our researchers at our institute, Dr. Mitch Turker for some answers. Dr. Turker has been studying the epigenome for many years. He received a PhD in pathology from the University of Washington as well as a JD from Lewis and Clark law school where you studied environmental law, here in Portland, Oregon. He's an avid hiker and enjoys all things outdoors in the Pacific Northwest. His research is focused on understanding how genetic changes occur and its relevance to cancer and aging.

Sam Greenspan: 00:54 Let's start by sharing with our listeners today what epigenetics is and how does it impact our work and health.

Mitch Turker: 01:01 So before I discuss epigenetics, so I have to talk a little bit about genetics in simple terms. So essentially we are products of our parents that we inherit genes from my mother and genes from our father. The mixture is really what makes us who we are. Epigenetics is a little bit different than just the DNA. It turns out that the DNA can be modified further. Mid Twentieth Century Conrad Waddington, and he wanted to understand what's called cell fate determinism. If you think about the fertilized egg, it's going to give rise to lots of different cell types in the body. We're going to end up with nerve cells, kidney cells, liver cells, blood cells. Obviously they're all different. They look very different. They function very differently, but they have the same DNA. And what Dr. Waddington was trying to really pose the question was why that occurred.

Mitch Turker: 01:51 And to explain it, he actually coined the term epigenetics. It means literally above genetics. It means literally above genetics, and years later scientists began finding a modification in DNA called DNA methylation. It's just a simple addition of a carbon with three hydrogens, certain residues on DNA, and that turned out to change gene expression. So that really is when we went from a conceptual
understanding of epigenetics to a molecular understanding of epigenetics. And the important thing is that the sequence is the same. So as I said before, a liver cell, it's DNA is going to be identical to the DNA in a nerve cell, but they're going to have very different patterns of DNA methylation.

Mitch Turker: 02:36 To kind of give an example of this, literally we'll go back about 250 years to Lanius. Lanius was the person who was characterizing all the different types of species and something that bothered him was a particular weed called toadflax. And what he found was that the toadflax had two different morphologies for its flowers. There was a common type of flower which was in an oval shape. And occasionally what he would find is that there was a variant of the flower which was kind of a close and almost looked like a pig's nose. It was disturbing to him because at the time he didn't know about evolution and he did not believe that one species could change at any way to look with a different appearance. What he said at the time was, this is if a cow gave rise to a calf with a wolf's head. That was the way he was characterizing the flower.

Sam Greenspan: 03:26 So was it just like the individual differences between the flowers because they had the same DNA, right?

Mitch Turker: 03:31 They had the same DNA in it, but it wasn't as different flowers, it was essentially some plants would have one type of flower and another plant will have a different flower. 250 years later, scientists found that the only difference that explained this was a particular gene called LYCY and what happened was in the closed flower, that gene was methylated, it had more DNA methylation than the same plant with the normal appearing flower. So this is a good example of epigenetics. It's simply a change in the modification to DNA. Everything else is the same. The DNA between these two planets would be identical, but flower morphology would change because of a particular gene was methylated in one flower than another one. What's been discovered in about the last 10 years or so is that the DNA methylation really creates what's called the epigenome. It can be modified by environmental exposures.

Mitch Turker: 04:23 So I talked before about the fact that there's genetics and epigenetics and now we can think about them as the nature and nurture and what's more important, what we inherit from our parents, or environmental exposures, so we have an explanation for both of these now. What we inherit from our parents is nature and our environmental exposures throughout our life and even in utero even before we're born, is the
nurturing part, which explains how our essentially our genetics are modified.

Sam Greenspan: 04:52
As someone with a minimal background in genetics this a lot for me to absorb. I gathered that through the epigenetic examples and flowers. You can see how the nurture side of the classic nature and nurture debate can have a lasting impact on genetics, your DNA methylation, environmental exposures, and how do these DNA changes translate to animal models and potentially humans? Can you give us a basic understanding and also share with our listeners an example?

Mitch Turker: 05:17
Sure. So animal models are commonly used, and particularly mice, in a lot of genetic research and now more recently with epigenetic research and one of the reasons is that it’s possible to change the genetic background and really to illustrate it I’ll give an example of an epigenetic model which has been used for about 15 years now and it's called the agouti mouse. So agouti is a code color pigment. The yellow changes due to agouti, and as the hairs grow at a particular point in development of the hair, a small yellow portion is a put down and what happens in the agouti mouse is a mutation which occurred because they get very fat. They inserted the front of the Agouti gene, because of that expression of the agouti gene is much harder than it should be. So these mice are yellow instead of brown.

Mitch Turker: 06:09
They're more prone to diabetes and cancer. And the cool thing is that if that little insert lies upstream of the gene gets methylated, gene expression goes back to its normal level and the mice look like they have a normal coat instead of the yellow coat. So, what'd you can end up with the litter in these agouti mice, brown mice, yellow mice, and what's called modeled, which have pigmentation patches of yellow and brown dispersed. And you can quantify how much of the modeling there is, how many yellow pups you get, how many brown pups you get.

Sam Greenspan: 06:46
So here we see an epigenetic example, DNA methylation can impact the coat color and health of agouti mice as well as the likelihood of passing on these traits to their offspring. I was curious what triggers DNA methylation and how much control we each have our own gene expression.

Mitch Turker: 07:05
These mice now we’re kind of used as an environmental sensor for in utero exposure. So for example, is a chemical bisphenol a usually just called BPA and it was in the news about five years ago.
Sam Greenspan: 07:15  Right. A lot of plastics, right?

Mitch Turker: 07:17  Plastics and stuff. And people were concerned that leaching out of the plastics may have an effect. And the Agouti mouse model demonstrated this effect very clearly because if you had a number of mice that were exposed in utero, that is in their mom, when the mom was pregnant, what it did was it drove more and more of the pucks towards the yellow phenotype, then the brown phenotype. So it was actually having an epigenetic effect because it was altering how much DNA methylation was laid down in that little insert upstream of the gene. So this is an example of how you can use a mouse model to demonstrate an epigenetic effect, and in this case, and an important one because a, the plastic was very common in use in most of the markets.

Sam Greenspan: 08:04  Right. So the bisphenol a?

Mitch Turker: 08:05  Yeah.

Sam Greenspan: 08:06  The BPA was creating the methylation.

Mitch Turker: 08:08  BPA was actually decreasing the methylation.

Sam Greenspan: 08:11  Okay. So what is the methylation mean with DNA?

Mitch Turker: 08:16  What the methylation means is that the beginning part of a gene is methylated, has more DNA methylation. It's not going to be expressed. A good example I can give you is in female cells, is two x chromosomes. One of them is inactive and the inactive x chromosome, all the genes on the inactive x chromosome have lots of DNA methylation, whereas their counterparts on the other x chromosome do not have DNA methylation. So in agouti mouse, what's happening, it's not an x chromosome gene, but it's the same principle. You can have one form and it's methylated and in a different mouse, the identical form that's not methylated, that'll drive the coloring between yellow and brown.

Sam Greenspan: 08:54  It sounds like the methylation has a huge impact on how the genes are expressed or which genes are expressed.

Mitch Turker: 09:02  And it's both.

Sam Greenspan: 09:02  Okay. I just wanted to try to clarify.

Mitch Turker: 09:05  It has an impact on gene expression and which genes, depending on which ones get methylated, or not methylated.
Okay. How can the epigenetics and the genomic processes help explain important behaviors like sleep as well? Some of our listeners may work night shifts or they might have nontraditional work schedules beyond a nine to five. How does this play a role in our genetic makeup over time?

To answer that actually, I'll continue with a mouse model. Then we can talk about people. So in this case, these are experiments that were done a few years ago by a European lab, and they were interested in can DNA methylation play a role in any changes in sleep behaviors or day night behaviors which are called circadian rhythms. And then what they were studying was a little tissue in the brain called a super cosmetic nucleus, which I'll just abbreviate to SCN. The important thing is that the SCN is the master clock. So what happens is every day when we see light, it kind of resets the SCN, the SCN coordinates with all the other tissues. So it's really the master clock coordinates with all the clocks in the different tissues. So everybody's on the same page, so to speak. So when we're awake our liver, for example, is metabolizing at an optimal rate, when we're asleep, the liver has calmed down and is metabolizing at a much lower rate.

This is the way everything is synchronized. And what they did was an interesting model where they took mice, just normal wild type mice. There was no genetic modifications and they changed them from a normal 24 hour cycle, which is 12 hours of light, 12 hours of dark to an 11 hour, really 22 hour cycle of 11 hours of dark and 11 hours of night. So this is counter, our normal biological rhythm is about 24 hours and this is forcing them to go on a 22 hour program and what they found is that when they took these mice after about a month or so on this it's 11 schedule and then put them back to a more normal schedule. They had a very hard time adapting back. They were kind of more stuck on 11/11 schedule and ultimately what they found is that's because genes in the SCN became methylated.

They changed their methylation patterns. So the reason it couldn't adapt back very quickly is because the methylation was changing gene expression in the SCN and that was making it more difficult for them to return back to the normal cycle of 12/12 or really a 24 hour cycle. And an interesting and a cool thing about this is that happened in young mice, but if you did the same thing in adult mice, they could snap back much more quickly from the 22 hour day to a 24 hour day because their SCN genes were not getting methylated, and this illustrates a principle which is that the epigenome on these DNA modifications occur much more easily early in life, particularly in
Utero as all the tissues are developing and the methylation patterns change and also when we're very young. But as we get older, it's somewhat more difficult for these changes to occur. It still occurs under certain circumstances. But in this particular one, the SCN, that plasticity it had to change methylation patterns is lost in the adults.

**Sam Greenspan:** 12:15  Right. So the younger mice are more susceptible to the impacts of a disrupted sleep schedule?

**Mitch Turker:** 12:21  Yeah, there they are, at least with this type of model. Now in humans, things so much more complicated, particularly people on shift work really are not fully on shift work. So somebody might work five days a week, you know, at night, and then the weekend they're going to try to get back to their other schedule, to a more daytime schedule because that's where the family is living, so to speak, in terms of when they were awake and asleep. So they're constantly going back and forth between these. And that's even potentially more disruptive. Dr. Steven Shea, who runs the institute, has done work with humans and what they did, where they put people in these laboratories, they desynchronize them. So every day their schedules were changing a bit and what they found is several weeks later when they looked at blood chemistry, these people almost looked like they were pre diabetic, which is consistent with the fact that people who do shift work are more prone to diabetes and obesity and cardiovascular disease.

**Mitch Turker:** 13:18  So Steve was able to mimic that in just a short period of time with people by disrupting their cycles. So it doesn't mean they were truly pre diabetic, but it shows you how you can start heading in that direction. So that has not yet been linked to epigenetic changes in these. And again, they're adults, but I suspect if they looked more carefully, some of these changes might be transiently epigenetic. It's one of the principals too, about epigenetic changes, it can go back and forth.

**Sam Greenspan:** 13:44  I'd imagine based on Dr. Shey's findings, it might not even be ethical to continue that type of study with humans given what it might mean for changes in their health.

**Mitch Turker:** 13:53  Well, it's an interesting question. And it wouldn't be ethical to do it long enough to actually cause disease states. But again, this is one of these things where you find out it's a problem and then you have to then change your experimental paradigms in the future or you can go back to mouse models where those type of ethical problems do not arise.
Sam Greenspan: Yeah. Another trending topic in workplace safety and health is stress, sleep and circadian rhythms. As we learned, are linked to methylation. However, sleep can also impact stress and it can lead to higher risks of workplace injuries. Can you share with our listeners about the current research we're doing in this area of sleep and stress?

Mitch Turker: So, I'll talk about, this work I'm doing with two colleagues, doctors Matt Butler and Chuck Allen here. And to explain this, I'm going to actually kind of increase our scope of what did epigenetic changes is to a little bit further. DNA is wrapped around proteins called histones and histones have little fragments or tails that stick out from them which can be modified and they can be modified also with methylation, histone methylation not DNA methylation, there's other types of modifications, but I'll talk about histone methylation, that was what we're studying. So it's a little bit more of the complexity. It's the same principle. These modifications help control gene expression and they also often work in concert with DNA methylation. And what we were asking is we're trying to get to this thing I told you before about the master clock and it helps control all the other tissues and we've been looking at the problem of what happens when you ... Can you separate these?

Mitch Turker: What we did in our experiments were, it's a very simple, again, another mouse model. We took mice that we're essentially on a 12 hour day, 12 hour nights schedule. Now, mice are active at night, not during the day like we are. And what we did was one time in a week we shortened their night schedule so they only got six hours of night and then they went back into a 12, 12 daylight thing. So essentially one day we turned on the lights after six hours of darkness and we looked in the liver and we initially were designing these experiments to do this once a week for a long period of time and then look at this particular methylation mark on the histones, which also corresponds to gene expression and we found a lot of changes. But the remarkable things we found when we looked earlier. So what happened was after only a few hours, and again remember the light comes into the brain, the liver doesn't see the light, would be a better way to say it.

Sam Greenspan: It's artificial light, right?

Mitch Turker: It's artificial light, but it's not going to get to the liver, but yet the liver was responding within three hours to the fact that the light came on. Because normally what happens is these methylation marks on the histones would go up and down, they
start coming up a little bit during the day, peak at night, and then come back down. What happened was when we turned the lights on, they stayed at that peak much longer than they should have, so it extended out the amount of time that the methylation mark was at its highest level. We were a bit surprised by this, so then we went and we looked at week later. So we just did again that single shift and we looked a week later because we knew a week later that the mice had gone back and they were now active at night again and essentially dormant during the day.

**Mitch Turker:** 17:17 And what we were very surprised to find was that the histone methylation mark, which should have been peaking at night, was still peaking during the day. And this gets back to the principal I was talking about it in terms of disruption. So now the liver is most active during the daytime, but the mice are most active during the nighttime. So we kind of separated that out and what Matt and Chuck and I want to do in the future, is start looking at how food influences this because Matt has shown that you can essentially flip the liver epigenetic changes by feeding them only during the day and not allowing them to eat at night. So we'll try to see if combination of food and light, first of all, how it disrupts it, and then secondly, how you can mix them, the food and the light changes to mitigate the changes which is really trying to figure out how to get back to the issue of shift workers, how to make it easier for them to stay on a good circadian cycle each day.

**Sam Greenspan:** 18:11 Right? Because the animal model is a stand in for these workplace situations where you had the night shift workers, right? And they're exposed to this type of light because they need to stay awake to do the work that they're doing.

**Mitch Turker:** 18:21 Exactly. They're totally reversed of what they should be. So again, putting it simply, the way we're going to try to do this is to figure out is there a way to give them, for example, a feeding schedule that will help them stay on a better ... essentially keep their brains in sync with their bodies.

**Sam Greenspan:** 18:38 Right. And plus you got to deal with the fact that workers are going to be more verbal about any additional stress that they might be having as opposed to an animal. It would be more challenging for them to stick to those schedules. Right?

**Mitch Turker:** 18:50 Yeah. The mice don't complain.

**Sam Greenspan:** 18:56 From the collaborative efforts of the researchers in our lab, Dr. Turker has summarized how changes in circadian rhythms can
impact gene expression and subsequent health, given that we each pass on our genes to the next generation. I was curious if these epigenetic changes impact their health in perceivable ways, like the Agouti mice. Through epigenetics, we know that these factors don't just impact your health. It may also affect the health of your children, grandchildren. There's even a Dutch study that I was reading that currently addresses epigenetics and diet. Can you tell us more about this study?

Mitch Turker: Sure. That Dutch study, I'll talk about it and then we'll talk about the implications of it. What happened was in the winter of 44, 45, essentially the Dutch were starting to aid the allies and that was angering German troops that were still there. And what they did essentially was they blocked and they stopped food from coming in. So it was an artificial famine, there was very little food in Holland and they went to very severe rations and a lot of people died from starvation during that time. Not surprisingly, some people who got pregnant or were pregnant during that time and what research has found out where, many decades later, the kids who were in utero at the time, particularly in the first or second trimester, not so much the third trimester, had very significant health consequences that you can actually measure these health consequences later. They died earlier. They have cardiovascular disease or diabetes.

Mitch Turker: So this was an example where you have an in-utero exposure, in this case famine, which plays out over many, many, many years. And recently scientists have begun looking at methylation pattern differences between these children and children born elsewhere. It's still controversial, but some of them are suggesting said some of the metabolic genes have been dampened down due to DNA methylation. And that's what makes it more difficult for these people over their entire lifetimes. So it introduces this concept which is called a DOHAD, developmental origins of health and disease, which gets to the concept that in utero exposure can play important role in how healthy you are or their risk for disease later in life. And the DOHAD researchers are now embracing epigenetics science, and they're starting to look at it. Kent Thornberg is on campus here, has really been the one who's been pushing out on campus because the best explanation for ... Remember earlier I said that when we're developing is when our epigenome is very flexible.

Sam Greenspan: Right. The younger that you are the more susceptible you are to these exposures in the environment.
Mitch Turker: 21:34

Exactly. So the concept is that the exposure is very early in life or during fetal development will get stuck at some point later on and stuck in the wrong way.

Sam Greenspan: 21:44

Is that part of the rationale behind the neonatal vitamins that a lot of pregnant women need?

Mitch Turker: 21:49

Yeah, the concept for folic acid contributes to the appropriate methylation levels, they think or at least the precursors to DNA methylation. And that is one of the reasons to believe that folic acid supplementation helps reduce the risk of birth defects.

Sam Greenspan: 22:06

And the research that you're talking about, it's called DOHAD, correct?

Mitch Turker: 22:07

DOHAD, yeah.

Sam Greenspan: 22:09

Is it possible to reverse these epigenetic changes?

Mitch Turker: 22:13

That is the hope. And again, one of the nice things about epigenetic changes as opposed to ... So for example, mutations are very difficult to reverse, but these epigenetic changes are reversible and scientists are actively trying to figure that out. So that right now the goal is to first figure out what these changes are and then possibly through different types of dietary supplementation later in life to maybe reverse them or at least reduce the types of changes. So that's what's thought about cancer biology is another place where this is actively pursued because cancer is a mixture of mutations and epigenetic changes and a lot of money being spent on epigenetic drugs to see if it's possible to treat cancers with these drugs to essentially reversed the changes in gene expression back to a more normal cell type.

Sam Greenspan: 22:59

Ideally there's prevention of exposure to these things, but then if that's not feasible for whatever reason, there's still hope with some of these changes that we've been talking about.

Mitch Turker: 23:06

Yeah. So prevention via and again, particular diets are better than other diets for prevention, but, but if the disease comes up, then you'd want to go to the secondary, which is to try to treat it with epigenetic modifying drugs.

Sam Greenspan: 23:19

In your field of work, you also studied the workplace exposures that can have impacts on worker epigenetic makeup over time. Can you tell us more about that?
Sure. So I'll talk a little bit about my own research funded by NASA because they're very concerned about the effects of space radiation from a trip to Mars or the moon colony type of things. And we've been doing some work in mice and really asking the question, and this is now in adult mice not in young mice, can radiation exposure change epigenetic patterns? And one of the first things we found, which was quite interesting was that if you expose a mouse to radiation, then you look in different tissues. First of all, we could detect methylation changes and they weren't random. You took all the DNA sequences and when methylation changes occurred and then mapped them, they would map to specific functions, really multiple genes would fit into a function. So is that specific in terms of metabolic pathways were being altered with DNA methylation.

And the most interesting thing we've found in these first experiments was that it was tissue specificity. So for example, in the heart, the genes and pathways that were modified. We're involved in cardiovascular functions. Whereas in the brain, the genes and pathways that modified were involved in the renal functions. So the same exposure in two different tissues elicited a very different response in the epigenome. And those responses are telling us that these methylation changes are somehow involved in reacting to the exposure and reacting in terms of the cell types. So the cell types of working specifically with what's important to them and it makes sense because a heart cell really doesn't really need to rev up or rev down on neuronal functions in order to deal with the radiation effect. And likewise the opposite for the brain doesn't need to deal with cardiovascular functions. So it makes sense in terms of understanding this.

But right now we have no idea of how these types of changes are occurring and that's what we'd like to do in the future. And so it really illustrates the principle that I said earlier that the environment affects us in ways that we had 10 years ago we never would have predicted. And some people are even now saying, if you think about our bodies and epigenome are now essentially recording all of our exposures over our lifetimes. It's kind of the physics principle that you can start somewhere and go all the way backwards and figure out what happened. And some people think now the epigenome is the same, that we could look at, in an old person, you can look at the epigenome and you can go backwards and predict all their life exposures.

Wow. That's like genetic Big Brother.
Mitch Turker: 25:58 Yeah. It's a bit theoretical obviously, but in principle, that's how it would work.

Sam Greenspan: 26:04 Wow. That's really interesting. A lot of the researchers in our lab are in the applied field or redesigned health interventions that really targeted these behaviors that we've been talking about. Do you feel like through epigenetics you can see these changes from adapting your sleep and your diet and your response to stress?

Mitch Turker: 26:20 Yeah, absolutely. I mean that's one of the nice things about this as I said before, is that these modifications are reversible, so if you think in terms of if you do something that's not good and you make epigenetic changes, the opposite is true too, a good lifestyle will create changes that are more consistent. Let's say for example with metabolism, everything working together in the right way. If you had bad behaviors. If you're eating not the right food, you're not exercising, and then you changed to where you're exercising more, you're changing your diet. All of those will have a positive influence and important concept is none of these things are necessarily totally established in our epigenome. It may take decades and decades of bad behavior to really change these things so they're irreversible. So at any point in time if you change your lifestyle to a healthier one, you lose weight, you change your blood chemistry to a better one, it will have a positive impact and just like, as I said, negative lifestyles will have a negative impact, positive lifestyle will have a positive impact, and they can help preserve, you know, what should be our optimal epigenome.

Sam Greenspan: 27:20 Through our research at the institute, we can help organizations become aware of how worker conditions can impact your health. Do you recommend any resources for any of our listeners might want to learn more?

Mitch Turker: 27:32 I don't usually make this recommendation, but if you Google epigenetics and wiki, it is really detailed and well written and I think for the lay person you can get a lot of information in that and a good understanding. In terms of a specific one, if people look for a video called ghost in our genes, which was produced by national public radio and can find it on YouTube. It was made some time ago, but it was when these first concepts about trans-generational effects were coming out, at least two of the scientists onto John Persia, I've known for a while, he's done a lot of work on epigenetics and aging and Randy Jirtle has been working with the agouti mouse model. I think if people have 40 minutes, that would be a really good place to find it again. It's called ghost in our genes.
Sam Greenspan: 28:14 Yeah, ghost in our genes. Awesome. We always like to end the show with a takeaway. If you can give our audience one takeaway on the public health significance of epigenetics, what would that be?

Mitch Turker: 28:23 Well, I think, you know, in a sense we've gone through it. We've talked about that we're a mixture of genetics, nature, nurture, and this is really the nurture side. So the nice thing that maybe we can do something about is we all eat, breathe, drink, we exercise, everything else. Also what we're exposed to, places we're living and now we're beginning to understand why that is. So you know, that's just kind of like a little guide in terms of it really does make a difference what you do because it's reflected now in potentially stable changes in the epigenome which could have important impacts on our health. But the other one which is the fascinating takeaway, which was really appreciated more recently as it might just not be what we do, but it might be what our parents do. For example, what a mother does and there's even study suggesting that is what our grandparents potentially do. There was a study from Sweden showing that what, what grandfather's ate or didn't eat can impact the health of the grandchildren. So in a sense, we can do stuff, but it's really looking forward. We need to take care of ourselves because it's going to impact generations down the road. It's not just our generations to generations before and the generations to come that are all effected by these modifications.

Sam Greenspan: 29:34 Yeah, it's a lot for me to think about next time I have a cookie and I want to have another one. It might have implications for my kids and the kids of my kids.

Helen Schuckers: 29:45 You're listening to What's Work Got To Do With It, your go to resource on all things, workplace safety, health, and wellbeing. We want to hear from you on workplace topics that you would like to discuss. Email us at occhealthsci@Osu.edu, subscribe to our Oregon and the workplace blog, or follow us on social media at Facebook.com/occhealthsci.ohsu or on twitter at ohsuoccheath to stay updated on current research resources, news, and community events. This podcast is a production of the Oregon Institute of Occupational Health Sciences and is hosted and directed by Helen Schuckers, Sam Greenspan and Anjali Rameshbabu. Thanks for tuning in.