The Effect of Nutrition on your Epigenetic Status Transcript

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Introduction and Guest Background

Hi everyone. I'm Doctor Sanjeev Goyal, and you're listening to the Pokemon Advanced Anti-Aging and Technology Summit. Today I'm interviewing Doctor Lucia.

Veronica. Doctor Lucia Cronica is a lecturer at the Stanford Prevention and Research Center, genomics lead at Meta Gen X incorporated, and editor of the peer reviewed journal by MD.

Her research investigates her diet, genetics and epigenetics, interact with each other to impact our health and longevity, and how to use this information to design personalized lifestyle interventions.

She's an acclaimed speaker and serves as an advisor for companies active in the personal genomics and precision health field. Doctor Monica received her PhD from the University of Vienna and has research experience from the University of Oxford, University of Southern California and University of Federico, two of Naples.

She has published research papers and top ranked peer reviewed journals such as Cell Genes and Development and the Embo Journal. I hope you enjoyed today's talk with her.

Hi everyone, I'm Doctor Sanjeev Goyal, and you're listening to the advanced Anti-Aging and Technology Summit. And today my guest is Doctor Lucia Araneta.

I'm already in the car. I'm great. Sanjiv, thank you very much for having me. I'm so excited to have you. I just, heard you talk to the academy that teaching physicians.

And I thought, it's very important for five years to listen to what, your expertise on this topic. So at first, if you can tell us, how did you get into the field of, epigenetics?

What was really why did you feel this is something you want to devote your life to? Yes. So, my interest, for epigenetics is a love story between the food and science.

I was born in Italy, where we value food as medicine, and, I, I decided to study, epigenetics, which was at that time, in the early 2000 and emerging science, and epigenetics.

Then the study of epigenetics really showed me how actually lifestyle can become biology. And, so I think epigenetics is the ultimate science for, for the bio hackers out there, because it provides a molecular explanation as to why, actually, our life exposure measures and actions can turn into biology, thus impacting our healthspan and lifespan.

And I've been so dedicating, the past 15 years of my career to this field, I, I first, did my PhD studies in, epigenetics in the University of Vienna.

At the time, I was studying one epigenetic modification, called Smaller RNase. And then I did a postdoc, at Oxford University. On another epigenetic modification called histone modifications.

And finally I, came to Stanford to study yet another epigenetic modification, DNA methylation and its role in, in basically lifestyle and medicine. Specifically, I'm looking at how DNA methylation changes after a lifestyle intervention involving a low carb and low fat diet within the diet fetus clinical trial.

What Epigenetics Is and Why It Matters

This is the largest, ever undertaken randomized clinical trial, looking at, weight loss and other, the disease risk,

biomarkers, during the course of, of, an intervention, a one year intervention with either a low carb or a low fat diet.

That's great. And was definitely get into that. But before we do, as you can just tell our viewers, what is it like if you explain epigenetics a little bit more in broad terms that they can get their heads around it is very healthy.

Yes, yes. So epigenetics epi means on the top. So on the top of our genes there are, molecular marks called epigenetic marks. And these marks act, like, a switch for genes.

They can turn genes on and off. And, this can explain, remarkable differences in the way our cells look. And perform, even without causing any genetic changes.

And that's why I told you before, epigenetics is the ultimate science for biohackers. You can explain why even if you don't change your genetics, you, through your lifestyle, you can change your biology because these switches, unlike genes, these switches dynamically respond to lifestyle.

And, and that's why you can think of, of your DNA as hardware and your epigenome, the entire set of your epigenetic marks as software that you can reprogram through your lifestyle choices and life life exposures.

I mean, the the power of epigenetics is so powerful that, for example, epigenetics can explain why you have the same DNA in each cell of your body, and yet every single cell looks different from each other.

So you have brain cells and skin cells that have the same genetic information, the same hardware. But because they they each use a different epigenetic software to tell the cell which the genes to turn on and off, they look so different from each other.

So that's that's so profound. That's that's telling us today that the most everything we're seeing is not the DNA level that's at the epigenetic level.

Yeah. The type is related to the epigenetic. Yes. And of course, this is not the only life style omics to explain why, you know, we there that's so genomics is, is set in stone.

Our genes, we can change our genes. But then there are other omics called collectively lifestyle omics, which can explain why lifestyle can actually change our biology.

And these are epi genomics microbiome proteomics and metabolomics. And these omics together express explain why you know lifestyle can become biology and affect our health.

So let's just you mentioning these epigenetic modifications and, and one of your study right now is looking at methylation, but you did mention two other types of modifications.

So, if you could just kind of just run through them and categories and, and why how do these modifications impact how the, the output is, which I guess is the proteins?

You know, that might be very helpful. Yes, sure. I will start with DNA methylation because it's the focus on my studies now. And that is the best studied modification, especially for lifestyle interventions and for a reason, because we have the technology to measure DNA, which lesion at high resolution.

And the, very in a very accurate, we so we can really tell you how much a gene is a methylated and which on which new nucleotide precisely before and after a lifestyle intervention.

And DNA methylation is the addition of a methyl group to the DNA itself, and specifically on the side two genes. Yeah. So your DNA is made of four nucleotides, and cytosine is one of these nucleotide, nucleotides and the, cytosine that are in the context of C, g, di nucleotides, so that these, cytosine and guanine, that di nucleotides in your DNA.

And when the cytosine is methylated, this is called DNA methylation. So basically DNA methylation is the methylation addition of a little group to your DNA itself.

Then we have some modifications. You some modification can be histone methylation phosphorylation ubiquitination phosphorylate. So the the phosphorylation that so many different marks that that are put on the histones.

What are histones. These are proteins that help coil the DNA inside your cells so that the DNA becomes compact. That it can fit the cell nucleus. But at the same time, it's accessible.

It's a it's compacted in an organized way so that, you know, the cell knows which genes are located where. So the the cell machinery can access those genes and turn the non on or off.

And the actually histones are so important because the reason why a gene is off is because it's so coiled with distance, it's so tightly coupled with distance that a gene cannot be open and read by the cell machinery.

So histones can control the opening of and closing of the chromatin.

DNA Methylation, Histones, and Small RNAs

So, to make, to turn genes on and off and, it sounds like that really, that's, that is the main mechanism of manipulating have histones, impact off of making, genes go off and on, which sounds like through methylation is one of the ways that things are being changed, which is that.

Yeah. Yeah. So, yeah. Exactly. So the opening and closing of the chromatin is the gateway to gene expression is the mechanism of epigenetics. You can regulate that either by directly leaking the DNA because then when you methylation disguise, the effect is that you recruit some reader protein that read the DNA methylation modification and open the chromatin there.

So it's a signal for the cell to come here and read me or come here and shut me down and close the chromatin. Or you can modify the histones. And by putting these marks on the histone in some of you, you achieve two outcomes.

The first outcome is that you can affect directly the opening and closing of the chromatin by affecting the electrostatic binding between mesons and DNA.

Because histones are positively charged and the the DNA is negatively charged. So when you modify stance, you directly affect this binding and opening and then on the top of that, like with the DNA methylation, the Isa modifications, work as a docking site for reader protein that comes and open or close the chromatin.

And then the the third, mechanism, are small RNAs and these are very complicated topics. I will briefly just say that small ironies, are an exciting way of, regulating the epigenome.

Micro earnings. Yes. So I'm using smaller RNAs because it's a broader term. Similarities does include microRNAs, which are the human version. Then there are I, I was working on other small RNA is that are called and in another way.

But anyway similarities and microorganism examples, similarities and why they're so exciting. Because these are basically mobile epigenetic marks. You can think of them like that because the similarities, are actually, they can shuttle between the cytoplasm and the nucleus.

And, and so they are more but they're, it's not like the DNA methylation results that are just around the DNA. And what they do, they help target either yeast, especially in some modification to specific loci.

Because if you think about it, how can a cell know where you are going to modify instance and how its more RNA

do that. So they can, can signal like the DNA methylation is the writer enzymes, the enzymes that it write, epigenetic modifications or your genes, they can act as a signal and say come here and mutilate this gene.

Or I'm making this other gene. And, yeah. So this is, this is a little bit the function of, why I need the second function is, to a, not to another mechanism.

So this is called transcriptional gene silencing, which means they, they, affect whether a gene is transcribed or not on or off. Or the more I may can also do something else, which is called the transcription gene silencing.

And it's also known as RNA interference. And this is another epigenetic mechanism by which actually there's more I need direct to target destruction of the mini, the messenger RNA after its production.

So after transcription, you produce an MRI and then this is destroys the post transcription only by small ironi and this is called the post transcription in silencing these perhaps too much detail, but I think it's an exciting field that is very good to hear that, because it's always more complex the more you dig.

Oh yeah, more complexity. There is. So let's not now that you kind of said, okay, that this, this DNA methylation is a marker of, you know, as a way for the for the modifications to happen epigenetic and, and this determines expression of, of of what turns out to be a phenotype, the way we look in our characteristics.

And this is lifestyles. You mentioned diet. But before we get to how we modify so generally this is the methylation is happening as we get older. I just want to talk a little bit about these epigenetic clocks that just living is causing methylation like just living.

And there's a certain amount of that is happening no matter what we want to do with that. Is that correct? Yes. So, let me go back. So methylation is a physiological process.

It's happening always. And actually it's a good thing that is happening without methylation. We couldn't live. So sometimes I get this question. Is there a good methylation and a bad methylation?

Actually, I wouldn't say that. I would say the methylation is always good, but when it goes wrong, he becomes bad. So it's, as you pointed out, with aging, what happens is that we have aberrant Mickey lesion, not only methylation in general, we have apparent epigenetic changes.

Because one important thing to just highlight here, we have we have seen that methylation is only one component of epigenetics. We have acetylation. Phosphorylation.

So many modifications. Moranis. But you know, all these epigenetic modifications including methylation get a little bit, you know, start to not working properly with age.

And that's why epigenetic alterations are one of the of the main hallmarks of aging. And now it turns out that because we can now measure epigenetics and DNA methylation so precisely in the last year, many so-called epigenetic clocks have been developed that that are based on DNA methylation and can measure, your DNA methylation twisting needs your age.

And the these called the biological age. So the age of your tissue stem cells and, fascinatingly, this biological age can deviate from your chronological age.

So you can be actually biologically younger or older than your chronological age, and that we now see that this reflects also your lifestyle and life exposures.

So that's that's very interesting. We're going to talk about some of these clocks. The first generation. Second generation. Oh yes. Yes that are so yeah that that so far there have been 13 published clocks, DNA methylation clocks.

And I'm sure there are many more under development now. So bye bye bye. Now, these, these information that may be outdated, and, I think one, first of all, we, the epigenetic clocks capture two different, type of information.

We have seen chronological age and biological age and, and you have mentioned the first generation and second generation clocks, mostly the first generation of clocks were focused, were trained, to predict chronological age.

Epigenetic Clocks and Biological Age

And so, I think the gold standard, for, for, of estimating a chronological age is, so far the Horvath clock, 2015, which has a correlation of, with, with chronological age of I think, 0.97 or something.

So it's very, very precise estimating chronological age. And and then, but then the if you think about it, we how useful is it to estimate chronological age?

We already have passports for that. Right. So, the, the, it can be very useful for forensic applications, for sure. You can really precisely track the, the age of, of, for of a forensic sample, for example.

But for us biomarkers, probably we are more interested, in, estimating biological age and how we can actually become biologically younger when we improve our lifestyle.

And, for this purpose, the second generation clocks are probably, you know, the, better options. And at least they are aiming at, estimating, biological age, better focusing on biological age and specifically really defining what biological age is like.

Biological age is actually a composite measure of different changes you can have, for example, and you know that then the health. So it is a measure of health, but you can have changes that explain, for example, whether your cells, become okay, and there some senescent, should we, you know, this part.

No, no. It's perfect. I'm just it's okay. Okay. It's excellent. Yeah. No, I was, wondering about this noises, but, in the. Okay. Okay. So, so the second generation clocks, instead are focusing on capturing biological age, and, specifically a recent paper by, Morgan Devine.

Describe how we can actually reconstruct, the various epigenetic clock to understand the which, epigenetic signals, captured by single clocks and, which of this signal, explain clean, differences in biological age and which type of biological age, for example?

We have some, second generation clocks that can, are better predicting, cancer. You know, the correlation with the cancer, progression or, the, the cells or, some other clocks are better in estimating cell senescence.

Other are better. And estimating mitochondrial dysfunction. All these, features are, are important processes in biological age. So even biological age is not one single entity for these reasons that there's not, one size fits all epigenetic clock.

There's not such a thing. Actually, epigenetic clocks are a composite measure of, biological age. And they also of course, correlate strongly with, chronological age.

And I think the future, the way forward, is really to develop like clock that, that focus on a subset of epigenetic signals that reflect specific biological processes connected with age me that be cancer cells, senescence, mitochondrial dysfunction.

Because I think these are the tools that we will need for precision medicine. We know that, you know, you may have you you may have actually a very strong mitochondrial function, but you may be starting developing from cancer cells.

And these are two different things and completely separate. That's what I was curious about is that we have, you

know, somebody could have, you know, do very well on one particular score.

I've seen like athletes come back with nine five year olds on a Corvette athlete. Oh my gosh, this is a this is a common theme on 15 years younger on a random score.

So I'm just befuddled. I'm like, I don't understand how that could be. How, how does this happen? So doesn't it normally happen that you're it's good if there's, you know, all these things are correlated, like, you know, if you do poorly in one area that.

This is exactly what I was talking about and why I think it's so important that we do studies where we, compare different clocks with lifestyle intervention in different populations, like even athletes.

So, I don't have, an answer for your specific question, like athletes. Why they are older on one clock. But my assumption is that there are some epigenetic changes, right?

That, for example, reflect, athletes trigger a lot of other measures. Right? They make damage, they trigger the way they produce damage while exercising.

And this damage actually used by your cell to trigger a positive adaptation that eventually make you live longer. But probably if you are measuring, like just the steady state of your epigenome, probably after exercise, you the readout may be an increase.

The oxidative damage and increase damage, signal that perhaps is captured by the clock as, an aging signal because the original clocks that were trained against chronological age are trained against recognize oxidative damage as an aging signal.

And so that's why I, I, you know, I think we are just scratching the surface of biological, clocks, in epigenetics because we do need the, like, different to develop different, more precise clocks for precise outcomes and populations.

Otherwise it's not going to be clinically useful. Yes, that makes sense to me. Let's go. Let's go. Right on to the lifestyle changes and what we understand about these things.

So far from the from the science. So I know that you're studying low fat versus low carb, because I get this all the time. And and I know there's some studies you're looking at.

Is that what genetic predispositions do we have that make us more suitable for one way or the other? Because that's the only thing that could potentially add more value to my to my patients or to the viewers.

Understand which way should they go? So do we. And do we know that at all? Like we have any further insight? Unfortunately not. So, so, first of all, let me, say that yes, genes can can modulate the way we respond to nutrients.

And this is called nutri genetics. However, the genetic effects on your response to food is polygenic. So there are many genes that do this job. And so testing one, 10 or 100 genes probably is not going to give you any accurate prediction.

For example, we did test in our study three genes that were had been shown previously to predict whether somebody was more likely, to respond to a low fat and low carbohydrate diet.

But we could not validate those previous reports, in our cohort. And the the reason is that probably we just tested three genes. That's not enough.

Diet, Genetics, and Precision Nutrition

And also, I think, these our study just demonstrate that genetic is only one component to assess clinically when

estimating your nutrition predispositions, you you need to assess other functional markers, your diet, your habits to come then to a more accurate prediction.

And this is called precision medicine. So for example for your carbohydrate tolerance we know that yes, there are a bunch of genes that can indicate that.

But then there are other metabolic markers that can be actually an indication of your carbohydrate threshold. This is called palmetto. Lake acid is actually one of these markers.

It is produced when we, actually eat carbohydrates as a first marker of the noble of Genesis from carbohydrates and it turns out that, for example, if you if your permit, oleic acid spikes up after you, eat carbohydrates yet you may have a lower carbohydrate threshold.

And then, you know, the powerful of combining your genetics, your genetic predispositions are just the starting line, your health journey. What what you start with those dispositions, but then you modify that with your lifestyle.

And so there are so other other markers, including metabolic markers and epigenetic markers. And I'm working on some, some of them that can can explain how your, life history, eating history and life exposures, exercise and shape changed your epigenetic have interacted with your genetic background to actually make who you are now.

And so that's that's what I call precision medicine, is the integration of nutri genetics, nutri genomics and other lifestyle omics to really individually and gradually catalyze every single patient and, target lifestyle intervention to their needs.

So is there a way so you're saying, there me, that we can't just look at the genes because it's, you know, probably ten 1520 how many genes that are and they're all coming into play.

So, what do you think we'll ever going to be able to understand that or will. I won't have to. We'll have to go at a higher level at, at the epigenetic level of protein, no matter what it is, I think.

So I think, I'm actually a believer we should just start already implementing some, think clinically. And that's part of my current work. And the buck just that will never be a standalone predictor.

So we can we can start small by including so what I'm doing now, I'm trying to really review all the clinical literature on we which genetic variants have been associated with which outcomes in the context of, studies that are tested, the response to specific diets or lifestyle interventions in the clinic in people, because this is also important, you the information that you see out there on the internet.

Yeah. About genetic association as no, systematic, review behind it. So when I, when I read that information, I don't know whether it comes from, an animal study, a human study, and you must studies.

It's an observational study just in, in a bunch of people with no intervention. Or it's a clinical trial. We need, first of all, that to really rank and give an evidence score for each genetic association in order to implement that in the clinic.

So this is the first step, I do believe. So to answer your question, I do believe we can do that. And I'm already working on this because I think it's a it's an important tool for clinicians and patients to see what their precise position are.

And just as a tool to pinpoint potential intervention needs, potential. And then once you pinpoint that and integrate with functional marker markers to see whether actually those associations are present or not, then then that's the power.

So I think we can we can start. So the first step is seeing what we are starting where we are now. But we already have many studies on the genetic interactions even in the clinic.

So let's just focus on them and use that information to validate even further those associations and other associations. And then and the next step will be as you as you mentioned, include the more genes in so-called polygenic scores, we already are there that in 2018, some studies were big studies were published, showing that, a polygenic score, including I think, 6 million snips in the, in the genome was able to predict, cardiovascular, disease with, with inaccurate AC comparable to monogenic, mutations.

And this is huge. This is just like, increasing. So you clinically, if we implement a tool like that, will be able to, increase, the prediction of patients that risks a risk 20 times and, is just like huge.

So the second step is going to polygenic score is adding more genes. And and then the third step is really integrating genetics with multi-omics epigenetics and other omics.

So I'm excited. I think we are already on the right path. And we can certainly do that in you know, you know, we we will make huge steps forward in the, in the next 5 to 10 years.

I'm sure it sounds like that. I mean, it's potential requires like, you know, huge massive supercomputer. It's not this is not simple. This is not something that can be just one way.

So if by one brain or whatever, this is something that requires massive data to look at the various interactions. And I know right now you have these, you know, these charts which okay, they assign a value of one per gene.

Look at the amount of these seven genes. Look at these. And so they are positive, you know five variations five out of seven. But that's assuming that each one has an equal contribution.

But it's probably not like that. You know, in the score actually, the the variants have weakened are weighted. Based on their assumed, weight, of significance in that in, association studies.

But I just want to, to say, okay, you are right. This is this is huge. This is perhaps, you know, it does require a ton of data, but we do have access now to huge datasets and biobanks.

So what I envision for the future is that we may just come with the, some candidate polygenic score, like the one for cardiovascular disease based on these, association studies, and then have, clinicians like you that then test these polygenic scores in the clinic in real world clinical setting with a granular information about other biomarkers, functional biomarkers.

And these will advance the field. Okay. So just, how much of is reversible, like let's say, somebody, you know, they're watching this say, look, you know, I just, taken care that much the last 20 years and, I'm interested.

But now, is it too late for me? How much of this, you know, actually, genetic changes are reversible. Yeah.

Reversibility, Reprogramming, and Longevity Medicine

So, I actually now, can, give you, an accurate estimate on, how quickly you can, reverse, those epigenetic marks with lifestyle, because just recently, the study was published, I think a couple of weeks ago, by Gerald and, moshinsky, and, they showed that we did a lifestyle intervention, involving, basically nutrient dense diet, and intermittent fasting and stress reduction.

You can, basically become two years genetically younger in just eight weeks. And that's an incredible thing when I saw that. But they used I mean, they was this for that five know is yes, they did use and I'm, I'm amazed.

You know, I, I don't know how I mean, I think you know, I'm, I think this a pilot study was in that I think 40 people. It's a small study. I'm just, excited by the potential.

I can tell you that there were there have been already many studies showing the reversibility of epigenetic changes. There are studies, done in the obese people that after bariatric surgery, can revert their epigenetic marks to the

lean type.

There are studies done in smokers that showing that smoking associated epigenetic marks can be reverted. Although it takes apparently six years, 15 years in medical school that this would take 15 years to revert back.

Yeah, exactly. Exactly. It's not done. Epigenetics makes. But we do have you know, we do have, many genes that these, these, changes can be reversed. And even in our study, we see a ton of changes in the epigenetic marks. And, also we look at some, epigenetic marks of diabetes, and they reversed after lifestyle intervention.

So, you know, this is not the first study showing that I was excited to see that this was a short study with lifestyle intervention and looking at, biological age.

But there are many, many hints that we can reverse, and, and, things for, for, for, yeah. In the positive direction. So is there a limit like, we I mean, physically, we still are aging.

And, so I just want to get your thoughts on that. What do you think? Do we think we'll be able to have an answer to actually, you know, like, actually, a stop or agent, is it a possibility for doing, DNA, epigenetic change?

It can stop epigenetic modifications. This is interesting. We can already do that in vitro. We can, through epigenetic reprograming. We can take a cell and then give the cell the cocktail of, of, reprograming factors and then reprogram that cell.

I can turn back the clock epigenetic and reprogram, that cell to an induced pluripotent stem cell. We can do that. And, we can, we can even only just transiently reprogram that cell in vitro so that it doesn't become essential, but think just rejuvenate.

We can rejuvenate in vitro cell with a cocktail of, reprograming factors. We can already do that. This is called direct reprogram reprograming or transfer reprograming.

And, and we can even, do a so-called trans differentiation, which means we are not actually catching the, the biological age, but we are just turning a cell into another skin cells into brain cells without changing biological age.

This is just to say we can precisely manipulate cell identity and biological age independently. In vitro know is huge. So we can do it. I mean, from scientifically it is possible now with the with lifestyle.

I think the concept of longevity medicine is, is, is an incremental and synergistic strategy to enhance first person, to focus on end of lifespan. So what I think it's we should really more think in terms of horizons for longevity medicine.

So or I think one is probably just increase healthspan and in the process perhaps extending also lifespan by implementing by focusing on lifestyle. And that, you know, just leveraging what we already have.

Discovery is already out in the field. And we already see that people are living longer, healthier. And and then I think duration two and three will require incremental involvement with multiple interventions and more.

But I risk interventions first tested for some diseases because of course in medicine the first principle is do not harm. So we want to test those high risk interventions with people that perhaps can benefit more and then extend to more people.

So I am very, very excited for the field overall. Yeah, it's such an exciting time. And, I thank you so much, letting people go to learn more about the work they do.

Yeah. So I, I, I'm not huge on social media. I do have a website doctor ironically.com I just post there some links to my, my courses. I do teach a class on the biology of longevity with with another Italian, Maddalena Dormouse.

She's the CEO, working on, on a company, for signals analytics. So, the compounds that killer sites and cells. But

anyway, so any kind of com, you can reach, you can contact me there.

There's my email address is some information about my, publications there on LinkedIn and social media. LinkedIn is, is a good, resource. And, yes. And, and, these meetings like this one, I, I love networking with clinicians, for, for promoting studies in the field.

This is great. I think what will work as time goes on and we can we have that I mean, I know, so, so, we'll talk to you soon. Thank you very much for being here.

Thank you very much for having me. And.