Introduction to Post-Transcriptional Gene Regulation

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And then we have those aggregation that are Alzheimer's, Alzheimer's, and that's one of the first connection. In fact, the publication we in 2009 was the first to have a connection between senescence and stress granule formation.

This is Dr. Talks, real talk from real doctors on the issues that matter to you most. All right, everyone. Welcome back to today's show. I'm so honored to be joined by Professor Ahmed Ghazouzi.

You are a leading expert in post-transcriptional gene regulation. It's a mouthful, but for all of you science folks out there, you're going to love this conversation.

And your pioneering work has truly advanced our understanding of micro RNA metabolism and its implications in muscle physiology, cancer. and aging-related diseases.

Right now, you serve as a professor of biosciences in the chair at the Center of Excellence for Smart Health at the King Abdul University of Science and Technology.

I am personally so thrilled to dive into this conversation with you today. So welcome. I'm glad you're here. Let's talk about your research and your impact in health span.

It would be my pleasure to talk to you. Thank you for the invitation. My honor to talk to you and your audience. Yes. Thank you so much. So, you know, I'm trying to decide how I want to jump into this because on the one hand, I guess we start with the big word post transcriptional.

gene regulation. So let's look at how your research focusing on post-transcriptional events helps to regulate gene expression. We've got experts and laypeople.

So break down in some simple terms why this is so important in looking at gene expression in this manner as it pertains to aging processes. So post-transcription regulation of gene expression is in a simple term, is the mechanism that links gene expression that happened in very defined location in the cell, which is the nucleus, and the machinery that will end up receiving the message from the genes, which is among other machinery in the cells, it's the translation machine which produce proteins.

So our DNA and the genes are located in the nucleus and they don't move. The DNA don't move anywhere. It's still steady in the nucleus. But to produce proteins and guide the cells to produce everything it needs, it needs to send messages.

And those are the mRNA molecules that you all know because of the pandemic. And those tiny molecules are produced in the nucleus, then sent away in a very protective manner to the cytoplasm to produce protein.

And that process between the birth of the MLNA to the moment reaches the machinery to be translated and translated, then eliminated. Because if MLNA stays longer than it should be, that's a problem.

That's the post-transcription regulation of gene expression. And there are a lot of mechanisms around that, very

well regulated, very coordinated. It's a busy highway, busy area of the cells.

I like, I like when we think of it like a busy highway, you know, I think it's important to, to be able to simplify some of these processes. And so how has this, so when you start to look at that busy highway and how things need to get delivered, what becomes important in, from an aging standpoint, what do you feel that we are having problems delivering?

We need to deliver more of. Is it just better communication of those proteins? So all of those really good questions that the field in general, many scientists work in various area of this process are trying to address.

But with time, during all of the lifespan, ourselves, for example, the majority of ourselves, when they are start multiplying, they have a finished capability to multiply.

Majority, more than 95% of ourselves, they divide.

How Stress Granules Form and Protect Cells

But after 50 or 55 division, they have to be eliminated. And that's, among other things, a process maybe many of you know related to Asian East Senate, since they sent us and they are eliminated.

Now, during our lifespan, this is a recurrent process to renew our blood cells, to renew many of our cells during injury, to renew our muscle cells. All of those are key.

However, with time during our lifespan and with aging, those processes that are needed to replenish our blood, to replenish to, let's say, regenerate our muscle of an injury or wound healing, et cetera, they start having difficulty being activated, et cetera.

And that's really the issue. How we maintain those processes longer and efficient. And post-transcription regulation turned out the last 20 years of research, we have clear evidence that that process is key for this to happen and to be maintained at longer.

Fantastic. So as we continue to dive into the cell and just what's happening at the small level to affect large system change, let's talk about your, I'm so excited about this.

Let's talk about your discovery of stress granules. We've all heard of stress, the stress response, fight or flight. It's a very important function in the body.

You know, a certain amount of stress is very good. It's what allows us to evolve forward and continue to thrive. And stress is good until it isn't, right?

When there's too many demands and not enough resources in the system to keep up with it. I like that. Yes. Thank you. Thank you. So what is a stress granule?

And what have you discovered about its role in this cellular stress response? stress granule when in early 2000, when I was doing my postdoc, we were asking the question whether this mechanism of gene, post-regulation of gene expression can really be impacted by stress.

That was really the question at the time. And something I did not know at the time, there is another lab at Harvard was working on the same questions.

And then together, The observation was when we exposed cells, various types of cells, to a given stress. At that time was heat shock when we started working with it.

The other lab was treating with arsenide, which is a very toxic substance that kills cells and creates. And both the observation was that foci or small granules are formed temporarily as long as the stress is there in the cytoplasm.

So the question was, what's their role? And that's how, and it was a very good observation at that time. And by reading each other's discoveries, we realized that we are really observing something very important in the physiology of the cell.

Then it turns out after several years of research, one of their role is really, it's that like us as an individual, as organism, When we have a stress, we react, whether we run, whether we crisp, or the cells the same way.

One of the main role is to protect vital players in the cell that will be needed to resume function the moment the stress is gone. And that's what stress is really an area where You gather RNA, you gather protein that are needed to be protected for time being.

Then it turns out they have a better, more roles that we are understanding more and more until now. The longevity revolution is about more than just searching online for a few hacks or any one of us moving our biomarkers in the right direction.

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Meet the people you want to make forever with. RadFest 2025. Take advantage of lower advanced pricing now at radfest.com. So I actually love this. I love stress.

I love the idea of how it is just a mechanism of just protecting us, taking care of us, and making sure that we can, all right, everything's safe, that's essential.

And how do we weather the storm, so to speak, rise to the challenge or buckle down. But I'm wondering, how do these stress granules, as you're seeing this phenomena inside of the cell, has there been a correlation to how this affects methylation?

So the connection with methylation is that methylation process, which is of course important for epigenetic marker and aging, are layers in leading to the recruitment of several proteins to the stress granule when they fall.

Now, if I go a little beyond this question and probably link the stress granule, what many scientists in the field think about them and related to region and age-related disease.

Now, I don't know whether you are familiar with another notion with what we call mRNA granules, which is the stress granule because the majority of their composition is mRNA.

As I said, mRNA are recruited with their protein protected. But there is another granule in the body that's very important in our brain. in our brain, in our actions that are coming from our brain to regulate muscle, to regulate the function of many.

In our brain, there are what we call mRNA granules that move along our actions that connect neurons to faraway targets. And those have the same composition than stress granules.

There are a lot of evidence that both are somehow connected and they both regulate protein production because one thing stress agrarian do in the time of crisis stress is they slow down protein production in the cell and they said you know we allow the production only those factors needed to combat stress to adapt to stress so now what we believe a lot of us believe is this stress agrarian form on a constant basis during normal lifespan and your lifespan.

Stress Granules, Methylation, and Aging Disease Links

However, if for any reason the formation and specifically the dissociation of his granul is affected, it could be related to some neurodegenerative disease such as Alzheimer's and others which happen with aging.

think about it is micro or picosecond of delay in the dissociation of stress agranum, with time, with decades, if it's accumulated, can lead probably to, at some point, freezing, and then we have those And that's one of the first connection.

In fact, the publication in 2009 was the first to have a connection between senescence and stress granule formation. Well, if you think about senescence, it's a stressed cell.

So it's putting out a SAP signal, right? So in essence, as it goes into that kind of twilight, as it's going into that limbo state, that the longer it's there, it can be pro-inflammatory in nature.

And I'm wondering if the signal itself is… So by definition is the cells that are at least under no condition is a cell that is finished It's ability to divide and become stressed, form reactive oxygen species among others, and they enter senescence, so they stop dividing.

Correct. That's the moment that happened, rightly so. There are signals come out of the senescence cells because they are metabolically active, bring the immune system and they are eliminated.

Those are in general senescence cells. But one of the things that connects senescence to aging is few of these cells throughout our lifespan go and hide within our tissues, and their number increase during our lifespan.

And like you said, you mentioned the SASP. The SASP, for those who are not familiar, is these are molecules, a group of molecules that are secreted by senescence cells and modify their niche, their environment.

Among other things that we found that the SASP can promote cancer progression and cancer metastasis, for example, specifically late in life. And they can also they are connected to neuro generative disease, such as Alzheimer, et cetera.

So the senescence is a phenotype where, but not always bad. Certain phenotypes, there are certain processes. For example, in our immune system, what we call some of our blood cells, basically lymphocytes, some of the lymphocytes need senescence to be produced, senescence during their present.

Wound healing needs senescence. Yes. So, and this is bring from, I don't know whether you are going, if we eliminate systematically all senescence, it's not necessarily always beneficial.

I agree. And I think I'm glad you brought that point up because I often speak to that. It's a very, especially in the longevity consumer market, you know, we hear about, oh, senescence, eliminate senescent cells.

No, no, no, no, no. Yes, you can do cycles to bring down the burden, like depending on the chronicity. What's the state of the system? Not everybody needs to go remove senescent cells, right?

So it's always for what reason? Just because something is founded in science, we see a correlative factor doesn't mean that that's what is needed in our system at this time.

So one other thing related to that. So I totally agree, senescence is not a synolithic or eliminating senescence. It's a good thing if it's targeted, it's done properly.

However, now the last few years, my lab participates in this little bit, I mean, with a couple of publications, is what we call instead synolytic, which are the drugs that completely eliminate senescence.

People are working on synomorphic, which is a way to close the ability or prevent SAS production by senescence, by keep the senescence phenotype. It is possible that's the way that probably to tackle these age and age-related, let's say, deleterious effects.

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If you're ready to join the Longevity Revolution, visit humanlongevityinstitute.com to enroll and become a practitioner today. Now I've also heard that there's some research, tell me if you're familiar with this, that there's some research going on that's looking at how senescent cells can in essence be reactivated.

into, especially if they've been, if they've been turned into a senescent state by way of saps signaling. So maybe we're talking the same thing. If we are able to stop that signaling, then they can function the way they're supposed to.

But if they've been turned into that senescent state by way of saps, that there could be a way to bring them out of that senescence back into regular.

This idea has been, it's not new. Yeah. the first observation that senescent cells can be reverted was published by the late God bless her soul Judith Campiz in 2003. So that was an observation where they showed there is a possibility to revert senescent cells.

Senescence, SASP, and Reversing Cell Aging

Now, what is done lately, I'm not sure that is something probably could be done systematically. Yes, that if you can turn off the behavior of sensitive cells, but even better if you can bring them back to healthier status, that would be something I think very beneficial.

Yes, could absolutely help our health expression for sure. Exactly. We have such limited time. We're going to have to do a follow-up conversation. I want to dive into your work around just muscle physiology, because that's so important as we look at aging.

So muscle, for me, the work, again, it's tried really the similar story than how I started being observing. I mean, interested in stress granule, discovered stress granule, co-discovered stress granule.

I was asked the question early on in my career, in 2001, when I started my lab, that what's the role of, if any, of post-transcription regulatory mechanism in muscle physiology?

And I was surprised that no one even asked that question in 2000, early 2000s. And then we had several observations tying RNA binding protein to really much they are needed for muscle physiology and needed for muscle development progression.

The flip side is we discovered during where we start asking the question, can these muscle fibers form stress granules to expose them to stress? And we observe a phenotype that I understood later because I did not know at the time that there are muscle atrophy and muscle wasting.

I see it in vitro in our petri dish. And then when I read the literature, it's really a big problem, which is muscle wasting, where as a result of many diseases, cancer first and many other diseases, you start wasting muscle.

And unfortunately, many of us have cancer patients that reach stage four. The best example happened, I remember, is Steve Jobs, if you remember. few months, I mean, couple years before his death was healthy, then appeared very skinny.

Pancreatic cancer is one of the cancers that trigger muscle wasting. And in fact, patients die not by tumors. Twenty to thirty percent of cancer patients die from here because they lose their muscle and they lose their muscle, they no longer able to breathe and they suffocate.

So that's the connection. And now we have evidence that some key players in post-transcription regulation can really be targeted to delay or stop muscle wasting.

And that's what we are working on now, as you speak. So what do you think about, what are you seeing with the use of full esthetics? Statin is a molecule, I mean, that has been used before.

The problem with statin and many other interventions where the idea is to increase muscle mass. It doesn't mean when you have bigger muscle that is a functional muscle.

And that's the problem. And there have been a lot of study with these agonists that early on in 2004, and there are clinical trial where, yeah, you can probably have intervene and have the muscle mass increase, et cetera, but it doesn't mean they're functional.

So. Are we able, so from a lifestyle standpoint, so let's say we are in a metabolic disease state. and the muscle is not functioning properly. Is there any level of physical activity and exercise that can help to signal proper function or do we need an intervention?

Okay. That's what is happening as we speak, is there an intervention with exercise regime and nutritional regimen. But those are specifically the issue with muscle wasting.

like an issue with age-related muscle loss, which is sarcopenia. Those two phenotypes, when they are diagnosed, it's almost too late. So problem number one that in the field we do not have yet is markers that you can identify early on to tell you this person is prone to muscle wasting if they develop disease X, Y, Z.

So that's one. The second thing is many treatments have been tried. For example, one of the driver of muscle wasting both as a response to disease or sarcopenia is inflammation.

Yes. So cytokines drive muscle wasting, a lot of them.

Muscle Wasting, Sarcopenia, and Regeneration

However, inhibiting cytokines, even at the group at the time, meaning, uh, inhibiting, let's say TNF alpha or others fail. One reason is because the enterprise are also needed for muscle formation.

Yes. Yeah. And professional functioning. So then now our, the research is focused more and more, at least for my love and many others like us is to identify really players that are at the end of the spectrum.

Are there factors when they are active? are connected directly trigger the muscle loss and can you turn them off? We have some hope there. So what if, what if you were, and are you looking at immune modulation?

So I think this is one of the things that happens a lot in research is we think it's, okay, how do I stop or start, right? How do I hinder? How do I block?

If we see too much cytokine production, then we should shunt that. And yet that you realize, well, that's not quite it also. So if we then think, well, wait, wait, wait, the way the body works is there's a natural response.

There are like, there's a modulation that's supposed to happen within the immune system. And so good is not always bad, bad is not always good. It's, it's, and also there's always a reason that the body's doing it.

So are you looking at modulation? That's exactly it. Because one thing during, One interesting phenotype, at least from a research point of view during muscle wasting, when cachexia hits and patients start losing muscle, one thing is a problem.

Our cells, the stem cells, what we call satellite cells that are in charge of regenerating muscle when they are lost, they still function. But their activity to recover the lost muscle with the rate of loss is in favor of the loss.

So one way is can we act on the existing or remaining satellite cells to do two things to make their activation better, stronger. and also block the loss.

Because for a long time, people thought that if we block muscle wasting, with the wasting, that's enough and the patient will recover. What we are realizing, blocking muscle wasting may not be enough alone.

So what you need also to find ways to trigger the recovery mechanism, regeneration mechanism, and that's Exactly what you mentioned. It is a metabolic intervention.

Yes. It is one of the metabolic organ, I mean, organ or machine in this body is mitochondria, which energy is produced. And in fact, in CACACTIC patient, it is really affected.

So if the intervention through that, and there are way in area of research that are very active in that, to how to correct mitochondria function and make satellite cells reactivated.

Yeah, absolutely. That's ongoing. I'm curious, what are your thoughts, if any, on the peptides? So like thymacin beta-4, for example. So we've got our thymogens, our thymic regulators.

So we've got like thymacin alpha is gonna help with modulation, but thymacin beta-4 is really shown to be able to help to stimulate proper muscle functionality and tissue repair.

Are you familiar with the mechanisms of action with that and your thoughts on it? time was in four. But I mean, that's exactly the way if we find there are a couple other molecules like GF15 and another molecule that is tried in that way, because others that have been tried 20 years ago failed, like statin, like you mentioned, etc.

Those are increased muscle, not necessarily functionalism. I think it's easy to have functional muscle. And I think that's the biggest part of the conversation folks is like remembering, yes, I think it's exciting to look at the research and understand that we're looking at very targeted ways for when we get into a state of dysfunction, yet we get to meet ourselves before that ever happens.

Meaning if we stay functional now, if we go out and work our muscles and move and continue to strengthen and to stretch and to hydrate and to nourish and to feed the body and the tissues, then we can offset, right?

We can slow down, hopefully, potentially that process. Absolutely. And in fact, I mean, I'm sure you and your audience heard about the rejuvenation science where we can rejuvenate some cells.

Yes. In fact, several research recent papers show that providing certain metabolites is enough to rejuvenate cells or reactivate them and make us a little younger in terms of behavior.

Absolutely. So as we get ready to wrap up, because I've only got a few more minutes with you, which this has just been a joy. What are you most excited about?

So in the land of research and the work that you're doing and the work that you've done, like even what you've already discovered, how do you see it all fitting together?

What you're most excited about is coming down the pike for expanding health spans. So for me, expanding have spent, I want really, and this is something personal and I'm developing this acts of research in the lab.

It's still in its infancy globally, but it's using bio gravity to address this question. Yes. Yes. Yes. So in fact, I mean, on that level, I mean, I'm lucky that the astronaut, the Saudi astronaut, Rayana decided to join my lab for her PhD.

Exercise, Metabolism, and Space Biology for Healthspan

And with Rayan, one project we are building, because let me, just to tease your imagination, is think about when astronauts go to the space, within a few days, they start losing their muscle mass.

And even if they stay for months, even a year, they lose their muscle mass and they still, but when they come back to Earth, within a few weeks, two, three months, they recover.

That tells us one thing. The loss of muscle in space mimics the loss of muscle in disease and mimics loss of muscle, specifically aging, in sarcopenia.

And as I told you, one of the issues is our satellite cells lose their ability to function during and under those conditions. In space, it seems the same way.

However, gravity or knockoff do something to our satellite cells that gives them the ability to regenerate faster when it comes to work. So that science and one of the projects I would like the question I'm trying to address and ask, what are the, let's say, mechanisms that allow adaptation from lack of gravity to back on Earth gravity?

Is there a way by understanding them, can we use them to rejuvenate our satellite cells and trigger the mechanism that will make muscle recover and waste even disease?

That's one thing that excites me. That is very exciting. And I mean, until then, stay in your rebounders, folks. That's we get milliseconds of anti going against gravity.

Right. But that is so beautiful. That's for me. It's really. And it's a simple question. Yeah. And when I ask it to colleagues, even from NASA, they really said that is something I mean, it's worth probably exploring.

It is because we're looking for ways. It's not just about staving off disease. It's saying, how do we really live better today for as long as possible tomorrow?

Happier, healthier, more vibrant tomorrows. And I would think that we can all agree that we want to be active. We want to be mobile. We want to be energized.

We want to look good. We want to feel good. That means we need our muscle. But also not only muscle. This tells me, even biologically, One key players in our health and maintain our health is our ability to adapt.

And more we understand the adaptation mechanism that we can trigger. It's better than go and either eliminate sick cells or do something. So if we understand and we maintain them functional longer, we can always rebound from one state to another back to healthier state, even if…

That's so yes, we can adapt. We can rebound. And so what I want to impart to everybody today as we get ready to close out this interview is remember your body is one expression of innate intelligence.

You were designed to literally adapt to the surrounding. Absolutely. Stress helps us learn about it. Like we take it in. We figure things out. We're like, okay, more of this, less of that.

But we get to do a better job of being the custodians of our health, which means in order to adapt and evolve and grow forward, we also need time to recover.

Exactly. So recovery is rest. It's taking some downtime. It's giving back what your body has been depleted of physically, mentally, emotionally, chemically, environmentally.

So it's a two way street. Thank you for the work you're doing in the research and looking and asking these really thought provoking questions. to be curious about how this human system works.

It's exciting, it's beautiful and sharing your knowledge. And remember, we get to do our part. So from top down in the research to bottom up within ourselves, thank you all for being here.

Professor Ahmad, thank you. It has just been beautiful. I appreciate you. I appreciate you. Thank you so much. Likewise. And everybody continue to stay bold, stay curious and express greater states of aliveness.

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