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Welcome to Yale Cancer Answers with your host doctor Anees Chagpar. Yale Cancer Answers features the latest information on cancer care by welcoming oncologists and specialists who are on the forefront of the battle to fight cancer. This week, it's a conversation about immunotherapies for cancer with Doctor Carla Rothlin. Doctor Rothlin is Dorys McConnell Duberg Professor of Immunobiology and professor of Pharmacology at the Yale School of Medicine, where Doctor Chagpar is a professor of surgical oncology.

Carla, maybe we can start off by you telling us a little bit about yourself. I was born in Argentina and it is in Argentina where I did all my initial training in science. I studied biochemistry in pharmacy at the University of Buenos Aires and did my PhD at the University of Buenos Aires. And interestingly, it was in a very different area of research.
My PhD was in Neuropharmacology. And then now almost 20 years ago I came to the United States. I came in particular to California to the Salk Institute, where I did my postdoctoral training, and it was there where I became fascinated by immunology and where I started to learn about immunology, and I know today we’re going to talk more about it, to talk more about it, and after doing my postdoc at the Salk Institute about 12 years ago I moved to Yale, where I started my own lab and I’m at the Department of Immunobiology. I’ve had a wonderful time here and I’m very fortunate to have been able to start my lab at this wonderful University.

So tell us more about what your lab does and what you study?

We are very interested in understanding the immune response. In particular, what we’re interested in understanding is what are the mechanisms that regulate how much the immune response will be. So how do you regulate the magnitude of the immune response? And also how long that
immune response will be?
How do you regulate the
duration of the immune response?
And as you can imagine,
understanding the regulation of the
magnitude and the duration has
tremendous implications every time.
They mean responses turn on,
so those are the
two fundamental features of the
immune response that our lab
centers around.
Right now when we’re in the
middle of this covid pandemic and
people are getting vaccinated,
I think a lot of people are thinking
about the immune response in terms
of vaccines and how long that
immunity from the vaccine will last.
Has your lab thought about that?
How do we gauge how
long an immune response will last
from a vaccine, for example?
That’s a very,
very interesting question.
When you think about the
duration of the immune response,
you would probably want to also think
how the immune system is built.
So it turns out that the immune system
in mammals, and in humans,
0:03:49.375 –> 0:03:51.5 has two big divisions.
0:03:52.697 –> 0:03:56.021 One, which is called innate and we are all
0:03:56.021 –> 0:03:59.15 born with that type of immune response.
0:03:59.15 –> 0:04:02.13 And it’s the very fast, quick response.
0:04:02.13 –> 0:04:05.105 And then there’s another one which is
0:04:05.105 –> 0:04:08.079 called adaptive and that is more tailored,
0:04:08.08 –> 0:04:11.48 more specific to each of the pathogens that,
0:04:11.48 –> 0:04:12.344 for instance,
0:04:12.344 –> 0:04:14.936 we can encounter when we’re thinking
0:04:14.936 –> 0:04:17.568 about the duration of the immune
0:04:17.568 –> 0:04:20.112 response in the context of vaccines.
0:04:20.12 –> 0:04:22.544 We are thinking that we really
0:04:22.544 –> 0:04:25.55 want to activate those cells of the
0:04:25.55 –> 0:04:27.725 adaptive immune system because they
0:04:27.725 –> 0:04:30.508 have the peculiarity that they can
0:04:30.508 –> 0:04:33.256 remember, they have memory and that
0:04:33.26 –> 0:04:35.45 is very important to understand.
0:04:35.862 –> 0:04:38.746 Our lab has focused primarily on trying
0:04:38.746 –> 0:04:40.989 to understand what regulates the
0:04:40.989 –> 0:04:43.677 duration of the more initial immune
0:04:43.677 –> 0:04:46.396 response of this innate immune response,
0:04:46.4 –> 0:04:49.19 and the reason why that is
0:04:49.19 –> 0:04:51.826 also very important is that
0:04:51.826 –> 0:04:54.065 a response is not so much
0:04:54.065 –> 0:04:56.442 directed to the pathogen to the
0:04:56.442 –> 0:04:58.827 microorganism that is infecting us.
0:04:58.83 –> 0:05:01.206 It can be broader and therefore
0:05:01.206 –> 0:05:03.296 can potentially have some
0:05:03.296 –> 0:05:04.598 adverse effects.
0:05:04.6 –> 0:05:05.378 For instance,
0:05:05.378 –> 0:05:07.323 inflammation forms part of this
very first innate immune response, so we absolutely needed to get the system going to get the immune response going which is absolutely required for inducing this immune response, but it cannot go on forever. So our lab has really focused on trying to understand what dictates the duration of this initial innate immune response. So when you talk about the innate immune response, is that kind of like if somebody got infected with covid, whether they produce a response against that, or is that still more the other longer term response where you develop a memory? It’s more the first type of response, so in our system, our immune system, is capable in that it can first recognize general changes. And let’s say maybe we are infected just with a bacterial, with a virus, right? And it can detect that and the cells that are involved in detecting that initially are the source of this first response. This innate immune response. That can detect that we’ve been infected with a bacteria or with a virus. Or with the fungi or parasite.
Now, as I was alluding to, there is this other more sophisticated adaptive immune response, and that takes a little bit longer to be triggered, is triggered by first the innate, and has that memory capacity. And what is beautiful also about this adaptive response is that it has the ability to distinguish which bacteria is infected. Or which viruses is infecting us. So just to take the example of a virus. For instance, our adaptive immune response to COVID-19 to SARS CoV2 will be different than, for instance influenza. So the adaptive immune response can distinguish that and our lab focused more on the very first response that realizes that you have a virus, but maybe doesn’t realize which viruses or realizes that you’ve been infected by bacteria, but doesn’t really realize which type of bacteria. But this first response is fundamental and the very interesting aspect of it is that we are born with it. That’s why it’s called innate. So as soon as we are born, we are able to react to these
microorganisms.

And then as we are exposed to them, we are able to induce this adaptive immune response. This learned response, that is the one that then will confer memory and that will be more specific.

Carla, when your lab studies this innate immune response, this initial response that hey, there’s something foreign in my body and that will help trigger the more adaptive response you had mentioned that you’re looking at, kind of the magnitude and the duration of that innate response, but it seems that the innate response is a little bit shorter than the longer term adaptive response. So how important is the magnitude and the duration of the innate response and why did you choose to look at that?

That’s absolutely a very important question. So of course my answer will be that it is very important and let me elaborate why. So in the field we have learned by the time we were starting to focus on trying to understand what regulates the magnitude and duration, we already knew a lot about
what triggers this innate immune response. And that was fundamental, right?
So we understood the rules by which the immune response is engaged, but as I was saying,
this is the very first response. It's the one that tells us all we have a bacteria or we have a virus
but cannot really distinguish between the type of bacteria or the type of virus and therefore is very broad.
It doesn't really help us to only attack the bacteria or the virus or the parasite and it also can't,
when a function is triggered, it can also induce what you could call collateral damage and it can affect your own cells.
The classical example is that inflammation is a key part of this innate immune response,
as you can imagine, inflammation can be very good to help eliminate pathogens,
but can also affect our own body. So we absolutely need this response when you get injured or when you have an infection.
But the problem is what happens if you react way too much or if you react forever, and so that became a key interest
of our lab trying to understand what dictates how much
you should respond so that you can attack the pathogen but not yourself and how long you should respond so that once you have eliminated the passage and you don’t keep on reacting against something that is not there anymore. So over the years we have been able to identify key breaks of the innate immune response. Why did you choose to look at the innate response and why is the magnitude and duration of that so important? As I was alluding, we require this very first innate response and at the time we started to become interested in understanding the regulation of the magnitude and the duration of the innate immune response, we already knew quite a lot what triggers this innate immune response. So that was fundamental work that allows us to understand that you need this response, but if features of this response as I was saying before is that it is triggered when, for instance, you encounter bacteria or a virus or parasite or fungi. But it’s pretty broad and therefore it not only reacts against the microorganism or the macroorganism,
but it can also affect your own self. For instance, a classic aspect of the innate immune response is what we usually call inflammation and so you can imagine that if this very broad immune response is way too high, or if it lasts forever, it can really induce what is known as collateral damage. It can really start affecting your own body, the way the system is built is that you kind of turn on this initial fire that then allows the induction of the more sophisticated adaptive immune response. But then you need to put off this fire, and that’s when these molecular mechanisms that regulate how big the fire will be and how long the fire will be come into play. And you can imagine that then they become very important. You really need to regulate how much and the duration, so that then you don’t start affecting your own self and this is what could happen in some type of diseases such as chronic inflammatory diseases or autoimmune diseases where you start affecting your own self.
And so as we think about the implications for cancer, I mean what you’re describing makes me think about things like hepatitis, where you can have hepatitis, which then causes inflammation and fibrosis and sets you up for hepatocellular carcinoma. Is that kind of the area that then brought you to thinking about cancer? Or where does the cancer angle come in? Yeah, that’s a very good analogy. So it turns out that absolutely, you have situations where you have this very chronic inflammation. This persistent activation of this innate immune response, and we know that chronic inflammation can absolutely increase the risk of some cancers. But the answer is not just so black and white. So what we’re starting to learn is that there are different types of inflammation. One like the one you described, very well known to increase the risk of cancers, but there are other potential types of inflammation, and this is actually the area of much.
ongoing investigation in the whole field.

What are the different types of inflammation that you have in cancer and how do they contribute to the concern and the analogy that I would make is that let’s say you sometimes want to induce a little bit of this fire to mount a good immune response against the cancer, but you don’t want to use too much that may be detrimental, so we are still at the level of trying to understand what are the different types of inflammatory responses in cancer and how they contribute to mount a good immune response against cancer or how they might contribute to actually favor cancer progression.

And so when you’re talking about mounting an immune response against cancer, it reminds me of things like immunotherapy. As we think about cancers and when we think about immunotherapy, we often think about revving up that immune system because so many cancers can hide from the immune system. So I wonder whether part of your
work has to do with immunotherapy.

But first we have to take a quick break for a medical minute, so please stay tuned for more information about immunotherapy and cancer with my guest Doctor Carla Rothlin.

Support for Yale Cancer Answers comes from AstraZeneca, working to eliminate cancer as a cause of death. Learn more at astrazeneca-us.com.

This is a medical minute about Melanoma. While Melanoma accounts for only about 4% of skin cancer cases, it causes the most skin cancer deaths when detected early, however, Melanoma is easily treated and highly curable.

Clinical trials are currently underway to test innovative new treatments for Melanoma. The goal of the specialized programs of research excellence in skin cancer or SPORE grant is to better understand the biology of skin cancer with a focus on discovering targets that will lead to improved diagnosis and treatment. More information is available at yalecancercenter.org.

You’re listening to Connecticut Public Radio. Welcome back to Yale Cancer Answers. This is doctor Anees Chagpar.
And I’m joined tonight by my guest doctor Carla Rothlin. We’re talking about immunotherapy for cancer and right before the break, Carla, you were telling us about the work that goes on in your lab. Really looking at the innate immune response and the magnitude and duration of that response and I wonder how that really pertains to cancer.

And right before the break, you mentioned that it’s not only thinking about the inflammation and collateral damage that can occur that may predispose patients to cancer, but it’s also in looking at the immune response that your body mounts against cancers, which makes me think more about immunotherapy.

So can you talk a little bit about how that works and what work you’ve been doing in that regard in your lab? When we think about the immune response against cancer, I think it’s very important to recognize that you know the immune response evolved to protect us against pathogens.

So when we mount an immune response against something that has changed in our body,
such as is the case of cancer cells, we’re going to go through the same rules. So as I was saying at the beginning, the very first innate immune response is absolutely essential for allowing us to mount an immune response, for instance to a microorganism. And it turns out that of course is going to be essential to mount a good immune response to cancer. Now when we start analyzing the immune response that the body mounts against cancer, we realize that there are a fraction of patients in which the immune response has effectively occurred, and probably during the years, it has tried to control that cancer, and so in those patients in which the immune response has occurred it could be that maybe now the immune response is kind of tired, many people refer to it as exhausted, and what happens is that those cells that have the memory, those cells of the adaptive immune response that can really go and kill the cancer cell right as they would have done if they were responding to a micronysm, now they’re responding to a cancer cell. They can become tired, and so a large fraction of the current immunotherapies...
are centered on reactivating those
for instance T cells, adaptive immune cells that have become tired, and this has been absolutely revolutionary in the treatment of patients.
So you can see how understanding the fundamentals of the immune response has translated into effective new therapies for cancer patients.
But it turns out that not all the patients have been able to mount a good immune response to the tumor. In some patients, there are no T cells to reactivate. They never were activated in the 1st place, and that’s where our thinking came in. That’s where turning on this you know, fire not too big, but turning it on a little bit might allow us to really keep the immune response against the cancer. And so a lot of current efforts in immunotherapy are centered on this initial response because we realized that in some patients it might not have occurred. And so we need to turn this on. Or in some patients it may also have gotten tired and we need to reactivate it.
Because I think when I think about cancer cells, I really think about normal cells that have gone awry, and so is it, perhaps that the body, especially in low grade cancers, cancers that look very much like normal cells, but that are just a little bit deranged that the body may not recognize them as being foreign. And how do you kickstart that innate response?

We’re talking about this very early stage, where cells are changing from being normal to abnormal right from this premalignant to malignant stages and again our immune system, the innate immune system is very sensitive to changes in the tissue. So instead of recognizing changes in terms of mutations that may have arisen in that cancer, Which is something that is much more recognized by the adaptive immune system, they can recognize if there has been a change in that issue. If maybe some cells are not functioning in the right way, and so those are things that we’re very interested in understanding at the molecular level,
what leads the activation of these innate immune cells? And then what is it that maybe changes that may appear like a wound that might affect the biology of these innate immune cells. Can you give us some glimmer into what those mechanisms are of actually kickstarting that immune system, because many of the people who are listening to this show are thinking, that’s great. You’re studying it at the basic science level. But really, where we are interested in going is how do we actually conquer cancer at a patient level and so can you give us a sense of what are kind of the molecular mechanisms that you’re looking at and how might we change those so that for actual patients we can potentially use this to make a difference? Absolutely this is where again basic science comes in. And I think this is where we need to understand fundamental biology. So the approach that we take is trying to understand what triggers this first response. To do this, we make use of models, sometimes it is not so easy to study this directly initially in a patient,
but we can take models where we can induce for instance the transformation of a cell or we can induce an infection and this is very important because as I said, the principles are going to be pretty much shared with the immune response to infection and so in these models which are in many occasions animal models, what we try to do is to try to detect how the cells of the innate immune system these first responders react to a cell that is changing either because there has been an infection and a wound or because it’s has been mutated and so we do this with advanced techniques that allow us to understand what is changing in the immune cell. Now a very important aspect I think is to then try to go to patient samples and understand whether those features that we saw change in the context of an infection or in the context of a model of cancer in an animal model, are also detected in the context of a transformation of a cell and the response to this in the patient. So I think going from this very fundamental basic approaches to taking some translational approaches and
trying to understand whether the same changes are observed is very important. But then again, I think we need to go back to the experimental models because once we understand what those changes are, we would like to intervene and modulate them so we can maybe turn on that fire a little bit more. Maybe induce that immune response a little bit more, and to do that again, we need to go to the model. So we start with the model, we validate and understand whether it is the same in a human setting and then we go back to the model to try to understand how we can change it to make it better. And it is this iterative type of experimental approach from the model to human samples to the model that has led to a lot of new ways to change the immune response and I am confident that we will allow us to understand what we need to change in those patients that have mounted an immune response to cancer. So tell us more about some of these interventions that you’ve tried and how they work in in the models and and what
prospects there are to actually having the same intervention in patients. And then just as a second piece to that question, when you talked earlier about this collateral damage, you wonder about when you actually take that into patients. Whether there will be collateral damage as well as you continue to light that fire, or whether you’ve really gotten it down to the point where you can modulate that very well to limit that collateral damage. Let me give you this with an example. So as I said, we try to understand what are those ways to regulate right? The magnitude and duration. And again, we went from the animal models to some human samples. And in doing that we identified genes that encode for molecules that are those regulators. And some of those genes and then those proteins that are encoded by this gene are a key focus of our lab and they’re called TAM receptors. Tyrosine kinase is the interesting aspect of this is, as I said,
they are like the brakes of this innate immune response. And these proteins can be targeted by drugs. So these proteins are in innate immune cells and when you activate this protein it will act as a break of this innate immune cell. It will put down this fire. What we can do is we can work and develop molecules that inhibit the function of this protein. Or we can also generate animal models that do not even have this protein. And so what you would predict is that if you do not engage this break so well, you will mount a better fire, so we will be able to regulate the magnitude of this response, and so that’s what we have discovered. And so going from the animal models to human cells, we now know that we can use small molecules that inhibit this proteins, and that allows a better fire. And we know that in animal models these can lead to the ability of these animals to mount a much better immune response against cancer. So we are actually right now at the process of starting to translate this
0:27:24.808 → 0:27:26.768 into humans through investigator
0:27:28.26 → 0:27:29.86 Actually here right here
0:27:29.86 → 0:27:31.86 at Yale Cancer Center,
0:27:31.86 → 0:27:34.646 so we can try to understand whether
0:27:34.646 → 0:27:37.44 these drugs, which we know are safe,
0:27:37.44 → 0:27:40.761 can ignite just a little bit more
0:27:40.761 → 0:27:44.219 this fire and you asked me the question,
0:27:44.79 → 0:27:46.785 how do I ensure that
0:27:46.785 → 0:27:49.286 it’s not a big fire that
0:27:49.286 → 0:27:50.718 will induce collateral damage?
0:27:50.72 → 0:27:52.27 That’s a very very important
0:27:52.27 → 0:27:53.51 question to answer.
0:27:53.51 → 0:27:55.37 I think that brings me back
0:27:55.37 → 0:27:56.61 to my initial training,
0:27:56.61 → 0:27:58.16 which was really in pharmacology,
0:27:58.16 → 0:28:00.02 in Neuropharmacology, but I learned,
0:28:00.02 → 0:28:01.88 I think a lot about pharmacology,
0:28:01.88 → 0:28:03.782 and that’s where drugs
0:28:03.782 → 0:28:05.29 give you the ability to
0:28:05.81 → 0:28:07.89 think a lot about the dose is the
0:28:07.951 → 0:28:09.907 regimens, how you’re
0:28:09.907 → 0:28:12.73 going to try to modulate this in vivo
0:28:12.73 → 0:28:14.28 and that becomes very important.
0:28:14.28 → 0:28:16.23 So how much you would give
0:28:16.23 → 0:28:17.83 of this drug may be
0:28:17.83 → 0:28:19.774 whether you will deliver it just
0:28:19.774 → 0:28:22.168 to the tumor site so you don’t
0:28:22.168 → 0:28:23.54 start a fire everywhere,
0:28:23.54 → 0:28:25.49 and that’s an aspect that will
0:28:25.49 → 0:28:27.221 be very important into making
0:28:27.221 –> 0:28:29.755 sure that this can truly help the
0:28:29.755 –> 0:28:31.468 patients eliminate the cancer and
0:28:31.468 –> 0:28:33.617 not induce fires in places that we
0:28:33.62 –> 0:28:34.628 don’t want to.
0:28:35.29 –> 0:28:37.516 Doctor Carla Rothlin is Dorys McConnell Duberg
Professor
0:28:37.52 –> 0:28:39.06 of Immunobiology
0:28:39.06 –> 0:28:40.6 and professor of Pharmacology
0:28:40.6 –> 0:28:42.71 at the Yale School of Medicine.
0:28:42.71 –> 0:28:44.864 If you have questions the addresses
0:28:44.864 –> 0:28:46.683 cancer answers at yale.edu and
0:28:46.683 –> 0:28:48.597 past editions of the program are
0:28:48.597 –> 0:28:50.562 available in audio and written
0:28:51.99 –> 0:28:54.662 We hope you’ll join us next week to
0:28:54.662 –> 0:28:57.276 learn more about the fight against
0:28:57.276 –> 0:29:00.072 cancer here on Connecticut Public Radio.