

### Transcript Details

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Asthma CSI: Behind the Cytokine Curtain, Part 5: A Mastermind Revealed

### Announcer

You're listening to *Asthma CSI: Behind the Cytokine Curtain*, sponsored by Amgen and AstraZeneca.

Part 5: A Mastermind Revealed

*[Doc and PI descend the stairs to Cipher's lab]*

*Doc (inner monologue)*

*We're on the precipice of a discovery. I can feel it.*

*The Pulmonary Investigator and I are on route to Cipher's lab. I've got a hunch that our inflammatory suspects are headed back to the Airway Epithelium, the scene of the crime itself. By now Cipher will have patched into the surveillance video feed installed there, which we'll need to catch wind of something the suspects don't want to share: a mastermind of this exacerbation.*

*One more try to get the Professor online; he'll want to see this.*

*[Doc dials and Professor picks up, fumbling a bit before speaking]*

**Professor (on the phone)**

Hello? Did I answer this thing correctly?

**Doc (shocked)**

Professor? I... can't believe you actually answered.

**Professor (on the phone)**

Oh, yes, well, I try not to make a habit of it. Say, did you know that asthma—

**Doc**

How fast do you think you can get down to Cipher's lab?

**Professor (on the phone)**

Good question! I don't know if you know this, but it's *quite* a trek getting down to that lab.

**Doc**

Trust me, I know that better than anyone. But we've got eyes and ears on the scene of the crime, and I think our suspects are headed straight back there. We could use your expertise right now.

**Professor (on the phone)**

Enough said. I'm on my way.

*[pause]*

I... take it they haven't fixed the elevator?

**Doc**

Very funny. See you down here.

*[Doc ends the call]*

*[Doc and PI enter Cipher's lab. Frothing beakers and beeping electronics are heard]*

**Doc (inner monologue)**

*The cluttered labyrinth that Cipher calls home seems even more frenzied than normal. There's beeping and buzzing escaping from every corridor, with Cipher, predictably, nowhere to be seen.*

**Doc (calling out)**

Cipher? Are you in here somewhere?

**Cipher (rolls in on a stool)**

Doc! I see you've brought our friendly Pulmonary Investigator along with you.

**PI (looking around)**

Wow, Cipher, you've carved out quite a lab down here. Nice bones to the place.

**Cipher**

Well, thank you so much. *[directed at Doc]* I'm so glad *someone* appreciates my thoughtful interior design...

**Doc**

*Anyway*, we just talked to the suspects, and I've got a feeling they're heading right back to the Airway Epithelium.

**Cipher**

What a coincidence, I was just taking a peek at the live feed. Follow me.

*[Cipher wheels away, Doc and PI follow]*

**Doc (inner monologue)**

*We enter a darkened room with a large monitor displaying various angles of video footage from the scene of the crime. One pointing outside of the Airway Epithelium shows some familiar Triggers and Insults still loitering around, while on the inside things are looking about as inflamed as when I left.*

*[Cipher pulls up two stools]*

**Cipher**

Here are some chairs. Don't mind all the books on them.

**Professor (in the distance; out of breath)**

Hello? Is anyone here? I seem to be lost again.

**Cipher**

In the video room, Professor!

**Professor (in the distance)**

You have a video room?

*[Professor swings around the corner, winded]*

**Professor**

Ahh, good to find you. For a while there I thought I'd never see the end of those stairs.

**PI (interrupting)**

Hey, check it out! There's movement on the screen!

**Doc (inner monologue)**

*All eyes fall on the image in front of us. It's a little fuzzy, but I can easily make out the silhouettes of our three suspects: Eosinophil, IgE-Producing B Cell, and Airway Smooth Muscle Cell. They gather discreetly near a quiet pocket of tissue lining, unaware of a few extra eyes and ears on their conversation.*

**Airway Smooth Muscle Cell**

All right, so we got a game plan, right? Cuz the Doc is hot on our trail and I think maybe I said more than I shoulda...

**Eosinophil**

Well that's an understatement, Airway Smooth Muscle Cell. But what's it matter? We did our part, we showed up for questioning. Now we just keep it status quo. Don't make any waves.

**IgE-Producing B Cell (worked up)**

"Don't make any waves"?! How can you be so blasé about this, Eosinophil? What's going to happen to the other cells working along our inflammatory cascade—the dendritic cells and the mast cells?

What's gonna happen to the innate lymphoid cells?<sup>1-3</sup>

**Eosinophil**

Pull it together, B. None of us are gonna take the blame. We've just gotta play it cool and lead her away from us.

**Airway Smooth Muscle Cell**

I think we should just say it.

**IgE-Producing B Cell**

Wait, you don't mean...

**Airway Smooth Muscle Cell**

Yeah, I do mean. We gotta point her to the top.

**Eosinophil**

The top? After all this time dodging questions, now you want to tell them who's been calling the shots?

**Airway Smooth Muscle Cell**

Look, what choice do we have? Way I see it, we have to face the facts. I was hyperresponsive throughout the exacerbation,<sup>4,5</sup> you left IgE antibodies,<sup>1-3</sup> and Eosinophil's proteins were *everywhere*.<sup>1-3</sup> Doc's coming for us either way. We've got to come clean.

**Doc (edge of her seat)**

Wait for it. Wait for it...

**Airway Smooth Muscle Cell**

We gotta tell her... it was TSLP that did it. TSLP is to blame.<sup>1-3</sup>

*[a beat, and then:]*

**Cipher (interjecting)**

TSLP! Of course! Why didn't I think of this *before*? Hang on guys...!

*[Cipher opens a drawer and copiously rifles through]*

I got it! I knew I had this tape somewhere.

*[She pops a tape into a cassette player]*

**Monotone Voice**

Thymic stromal lymphopoietin, or TSLP, is a key epithelial cytokine in asthma pathophysiology.<sup>1-3</sup> At its position atop the inflammatory cascade, TSLP initiates multiple downstream innate and adaptive immune responses involved in asthma inflammation.<sup>1-3</sup>

**Doc**

Just like the Tail who followed me outside was saying... someone all the way up at the *top*—

**Cipher (shushing)**

Shhhhhh.

**Monotone Voice**

For patients with severe asthma, overexpression of TSLP can result in pathologic inflammation, which can cause worsening of asthma symptoms and exacerbations.<sup>1-3,6</sup> In fact, multiple clinical features of asthma have been associated with higher TSLP expression, including asthma severity,<sup>7,8</sup> reduced lung function,<sup>6,8</sup> potential airway remodeling,<sup>9,10</sup> reduced steroid response,<sup>11</sup> and exaggerated T2 response to viral infections.<sup>12-14</sup>

**Cipher**

You see? It's TSLP who's been calling the shots this whole time!

### Monotone Voice

We hope you're enjoying *Asthma After Dark*, the program for—

*[CLICK. Cipher whacks the stop button on the cassette player]*

### Cipher

That's enough of that...

### Professor

Yes! How could I not have seen this before? *Of course* it's TSLP! Those suspects brought in were just downstream effector cells. They never had the capacity to inflict that kind of inflammatory chaos alone!<sup>1-3</sup>

### Cipher

It all makes sense. The granule proteins from Eosinophil; the trailing antibodies from IgE-producing B cell; the hyperreactivity from Airway Smooth Muscle Cell. TSLP has been an instigator working behind the scenes all along!<sup>1-5</sup>

### Doc

And that means that what we saw at the scene of the crime – the airway hyperresponsiveness, the mucus overproduction, potentially even the airway remodeling – those must have been some of TSLP's calling cards via downstream inflammatory effects.<sup>1,9,10</sup>

### Professor

Right you are. Downstream cascades from an upstream catalyst, if you will. And I hope you will, because that's catchy.

### PI

Heh. Well I'll be. This TSLP fella sounds like the real deal!

### Professor (to PI)

I'm sorry, do I know you? Are you one of the basement dwellers like Cipher?

*[loose banter breaks out among the group. Doc reflects]*

### Doc (inner monologue)

*And just like that, my team has done it again. The pieces of the puzzle start to come together.*

*I've been looking at this case from the bottom-up, when I should have started at the top. This case of severe asthma inflammation couldn't have been a one-cell job, and our suspects were proof enough of that based on the parts they played. But an inflammatory cascade like this needed someone calling the shots, and that someone appears to have been TSLP.<sup>1-3</sup>*

*Time to track this mastermind down.*

### Doc

You guys stay here and keep your eyes on the suspects. Where they go, TSLP may not be far behind. I'll head back to the Airway Epithelium. Maybe someone or something will lead me straight to TSLP.

### Professor

Seems logical.

### Cipher

Give us a ring if you need anything.

### Doc

Will do.

*[Doc leaves, closes the door behind her, and goes back up the stairs]*

### Doc (inner monologue)

*TSLP has been puppeteering this airway inflammation from the start,<sup>1-3</sup> so it's gonna take some out-of-the-box thinking to track him down. Maybe coming back to the scene of the crime, where the case began, will catch him off-guard.*

*[Doc crosses the lobby to head out]*

*TSLP may be used to playing in the shadows, but this time I plan to shed some light where it's most—*

### Phil

Hey Doc! Wait!

*[Phil jogs over to her]*

**Doc**

What's going on, Phil?

**Phil**

Someone's here to see you. I've never met him before.

**Doc (short)**

I don't have time for making new friends right now, Phil. I've got a culprit to catch.

**Phil**

Well that's just the thing, Doc. He says he's a good friend of yours already, though honestly, he seems kinda like a bad egg to me. No offense.

**Doc (cautious)**

None taken. Who'd this "friend" say he was?

**Phil**

He calls himself "TSLP." Came in here like he owned the place. He's signed in and waiting for you.

**Doc (inner monologue)**

*Change of plan. The mastermind I've been looking for this whole time has now found me...*

**Announcer**

You have been listening to *Asthma CSI: Behind the Cytokine Curtain*, sponsored by Amgen and AstraZeneca.

Join us next time for Part 6: TSLP Unmasked

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