

Transcript Details

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Asthma CSI: Behind the Cytokine Curtain, Part 6: TSLP Unmasked

Announcer

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

Part 6: TSLP Unmasked

[Doc stands in the center of the front lobby of Asthma HQ, reeling from the news she just heard.]

Doc (inner monologue)

This case of severe airway inflammation has been anything but easy. I've been traveling back and forth through the rain, climbing up and down endless stairs, coming at this case from every angle to find answers for our patients. But it turns out that the culprit I've been looking for all along, a shadowy mastermind known as TSLP, has come and found me on my own turf.

Phil, attending the front desk of Asthma HQ's lobby, is standing in front of me with a nervous look on his face.

Doc

Phil, why do you have such a nervous look on your face?

Phil (nervously)

Well...that visitor who came in looking for you, going by the name of TSLP? I may have sorta directed him to wait for you in your office.

Doc (incredulous)

Phil, you mean to tell me, our primary suspect for this severe asthma exacerbation is now waiting for me in my office? Unattended?

Phil

Sorry, I panicked. He seemed pretty sure of himself.

Doc

I'll bet he did. It's alright, Phil. I've got the home field advantage this way. *[walking off, calling over shoulder]* Well, off to see the wizard, so to speak.

Phil (calling after her; serious)

Good luck, Doc!

[Doc heads over to her office]

Doc (inner monologue)

My heart pounds as I head toward my office, and this time it's not because I'm climbing lots of stairs. I'm finally coming face to face with our hidden nemesis.

The office door is slightly ajar and I peer in, catching a glimpse of TSLP before he notices me. He's leaning over a file cabinet to read a newspaper clipping from a couple of months ago, with a headline that reads—

TSLP

"Doc Infiltrates Environmental Insults, Safeguards Airway Epithelium from Exacerbation."

You must be pretty proud of yourself, an achievement like that.

Doc

Takes a village. And I take it you're TSLP, so let's cut the small talk and take a seat.

[Doc steps in the room and closes the door behind her. She sits behind her desk.]

Doc (inner monologue)

TSLP turns and gives me a sly, practiced smile. As he moves to sit in the chair opposite my desk, I notice something in his hand – an eosinophilic granule protein. That's mighty familiar–

TSLP

We meet again, Doc.

Doc

So we do, TSLP. But this time, in a more conspicuous location than the alley I managed to corner you in.

TSLP

So you did, Doc. So you did. I guess you could say I'm here to return the favor.

Doc

Think you have me cornered in my own headquarters, do you?

TSLP

I'm just here to fill in some of the blanks. And based on everything I've seen, you and your team may need it.

Doc

Well lucky for me, you haven't seen everything I've seen. But enlighten me, TSLP. How do you factor into this case of severe asthma?

TSLP

Mind if I pace around? Helps me think.

Doc

By all means. Just stay in front of me while you do it this time.

TSLP

I take it you know by now that I'm at the top of the inflammatory cascade in asthma pathophysiology¹⁻³.

Doc

I do. As a key epithelial cytokine in asthma, you're the talk of the town¹⁻³.

TSLP

That I am. But I'm just warming up, Doc. You see, I've been watching you and your team trying to get to the bottom of airway inflammation since this case began. I'm here to remind you, once again, that sometimes, in this topsy-turvy world, a good way to get to the bottom of a mystery is to look to the top. That's where I hang *my* hat with severe asthma¹⁻³.

Doc

I'm following.

TSLP

And from the top, I can initiate multiple downstream innate and adaptive immune responses involved in asthma inflammation¹⁻³.

Doc

Like the work of some of your downstream cronies: Eosinophil, IgE- producing B Cell, and Airway Smooth Muscle Cell. They were taking orders from you¹⁻³.

TSLP

So you talked to them after all. I told you they weren't the ones you were looking for. Should've saved your breath on them, Doc.

Doc

Tell me, TSLP, do you get lonely at the top? Tired of pulling the strings on severe airway inflammation from afar and not getting recognized?

TSLP

Oh I'm not quite as far off as some think. I hail from a variety of sources, epithelial cells being the major one. But other sources include

mast cells, dendritic cells, fibroblasts, and even airway smooth muscle cells just like one of your suspects¹⁻⁹.

And just to set the record straight, I don't get jealous of downstream effector cells. They can't spark the kind of inflammatory changes I can from where I'm perched¹⁻³.

Doc

And yet, here you are, pacing around my office with an axe to grind. But I digress. You were talking about the downstream effects.

TSLP

How much time have you got? I'm a driver of quite a few manifestations of asthma pathogenesis, if I do say so.

Doc

Indulge me, TSLP.

TSLP

Airway hyperresponsiveness, for starters. It's *my* cytokine signaling that leads others in the inflammatory cascade to activate B cell IgE production¹⁰⁻¹² and mast cells¹¹, as well as airway smooth muscle contraction^{10,12}. The end result?

Doc

Airway hyperresponsiveness, I heard you. You're neglecting I was at the scene of the crime. I saw the constricted airways^{10,12} and antibodies littering the place¹⁻³ for myself. And I spoke to those two pawns of your inflammatory cascade. You'll have to give up more of your schemes if you're trying to surprise me, TSLP.

TSLP

How about increased mucus production^{10,12}? Vascular permeability^{11,12}? Epithelial barrier dysfunction¹³? You think those effects of severe airway inflammation just happen by themselves?

Doc

I don't, and I know your part in that now. But I also know more than you're telling me.

TSLP (cautiously incredulous)

Oh do you? Well, your turn, then, Doc. Indulge *me*.

Doc

I know that *multiple* clinical features of asthma are associated with you, TSLP, including asthma severity^{5,14}, reduced lung function^{14,15}, potential airway remodeling^{16,17}, reduced steroid response¹⁸, and exaggerated T2 response to viral infections¹⁹⁻²¹.

TSLP (surprised)

You.... knew all that, did you?

Doc

I'm just warming up. Sound familiar?

Doc (inner monologue)

TSLP stops pacing and looks at me in a new way. I might be getting warmed up now, but from the look on his face, he's the one who's starting to sweat.

Doc (stern)

Let's level-set. You were so busy chasing my tail, you didn't really notice me and my team pursuing yours at the same time. But now that I've gotten *your* measure, I think it's about time that you've gotten *mine*.

We've known from the start that managing asthma is challenging because airway inflammation is complex, heterogeneous, and dynamic²²⁻²⁴.

But since then it's also become clear that you *do* act at the top of the inflammatory cascade¹⁻³. And maybe sitting in that high chair has made you sloppy, because it turns out you're also overexpressed in patients with asthma^{5,14}, and that overexpression connects back to multiple aspects of asthma pathophysiology^{1-3,15}. Am I missing anything so far?

TSLP

....n.. no?

Doc

Good. Then I'll get to the point. This case has put a big, bright spotlight on you, TSLP. Maybe that's what you think you wanted, but now you've got it. And know this: all eyes are on *you* now...

Doc (inner monologue)

Bingo. TSLP looks like he's had the wind knocked right out of him. Fitting, considering his role in the crime of severe airway inflammation. He sits back in his chair, deflated.

TSLP (bargaining)

Maybe we could... work out a deal, you and I.

Doc (scoffing)

How's that?

TSLP

You cracked this case, but I helped you along the way. I can do that again. You solve some more cases and become a star in this town. Meanwhile, I get some... let's call it, *diplomatic immunity* for my troubles. Consider it a win-win.

Doc (skeptical)

Diplomatic immunity?

TSLP

Yeah, I keep you in the loop on what I'm doing, and you give me a little bit of leeway to.... *exacerbate* things from time to time. What do you say?

[Doc pauses]

Doc

No deal, TSLP.

TSLP

No? We could make a good team.

Doc

Figuring you out was just the first step. And unlike you, I'm not in the business of leaving asthma patients behind.

TSLP

That's too bad, considering I found *you*. Twice. What makes you think I won't disappear just as easily?

Doc

You may believe you can stay hidden, but don't forget: I don't work alone. I've got a team of investigators behind me on every case. And what we learn together, the rest of the asthma care community learns alongside us. So I wouldn't get too comfortable in that high chair you sit on in the inflammatory cascade. Not if I were you.

[TSLP stews on this for a moment, gets out of his chair, and walks toward the door]

TSLP

This isn't the last you'll hear of me.

[The door opens]

See ya around, Doc.

[The door closes]

Doc

I'm counting on it.

Doc (inner monologue)

I take a deep breath to steady myself. This confrontation wasn't easy, but it had to happen. There's so much more we need to do for our severe asthma patients, but shining a light on TSLP is a critical step in the journey. For now, it's time to assemble the team—

[Sounds of shuffling and muffled talking are heard outside the door]

—Then again, from the sounds outside my door, I'd wager the team has assembled already.

[The door opens and Cipher peeks her head through the doorway]

Cipher

Doc! Was that TSLP who just hightailed it out of here?

[Professor chimes in from just outside the door]

Professor (distant)

Ask Doc if that was TSLP!

Cipher (to Professor)

That's what I'm doing!

Professor (distant)

Tell her / think that was TSLP.

Doc

Come on in, team.

[A crowd of people shuffle into the room, chattering in quick succession]

Cipher

I can't believe that was really *him*!

Professor

All the telltale signs, really.

Phil

I don't think he's Doc's friend at all!

PI

I could take him.

Doc

I had a feeling you'd all be close by. Thanks for having my back.

Cipher

Like we'd miss out on that for anything! So, what happened? Did you stick it to him?

Doc

Let's just say he'll think twice before he waltzes in here again, knowing the whole of Asthma HQ is now laser-focused on TSLP.

Professor

Well *that* seems fairly obvious. He practically ran out of here, he was so scared. But the most important question that follows is what's next? There are asthma exacerbations happening all over town, and this case, like so many others, stemmed from inadequately controlled asthma²⁵⁻²⁷.

Cipher

Professor's right. Many patients do remain inadequately controlled with ongoing symptoms and exacerbations²⁵, which is bad news for keeping the calls that come into Asthma HQ down.

Phil

And I'm just the guy who answers those calls, but it seems to me poorly controlled asthma is associated with decreased quality of life²⁶, increased oral corticosteroid use²⁷, and increased healthcare resource utilization²⁸...but what do I know?

PI

Geez, Phil, you could give the Professor a run for his job with a memory like that!

Phil

Hey, thanks, PI!

Professor

Yes, well, anyway, as I've said before, there's far more yet to learn about the nature of asthma and airway inflammation. But after the way you've all handled this case... I know our team's up for the challenge.

Doc

Couldn't agree with you more, Professor. Let's take it one step at a time.

[Suddenly, Phil's phone rings]

Speaking of which...

Phil

Asthma HQ, Phil speaking.

[A pause]

Is that so? Yeah. Alright, I'll let them know.

[Phil hangs up]

Gang, looks like we've got another severe asthma exacerbation in progress. And from the sound of it, this might be a tough one to crack.

Doc

Let's go.

[The team moves purposefully toward the door and walks out]

Doc (inner monologue)

And just like that, we're on the move. I've got a strong hunch that TSLP played a leading hand in this asthma attack as well. But after today, there's nothing my team and I can't tackle.

Asthma culprits, beware... we're back on the case.

Announcer

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US-56457