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Asthma CSI: Behind the Cytokine Curtain, Part 3: The Tail

### Announcer:

You're listening to *Asthma CSI: Behind the Cytokine Curtain*, sponsored by Amgen and AstraZeneca.  
Part 3: The Tail

*[The sound of two sets of footsteps on wet pavement is heard as Doc makes her way back to Asthma Headquarters. Doc's footsteps pick up the pace as the second set of footsteps grow closer]*

### Doc (inner monologue)

*There it is again. A second pair of footsteps. And they're closing in. Whoever it is, it's keeping to the shadows – a seasoned Tail.*

*I'm nearly at Asthma HQ. I could make a run for it, but then I'd lose the chance of finding out what this mystery walker knows and wants. I'm being tailed for a reason, and I've got a hunch that it has something to do with this case of severe inflammation at the Airway Epithelium. There's no such thing as coincidences in my line of work, so I take every lead I get seriously.*

*[Doc stops briefly, then sidesteps in another direction to head into a nearby alley.]*

*I see a small alleyway to my right. I pivot and I turn into it, then quickly duck behind a small alcove. There are nooks and crannies to hide in all over this city if you know where to find them.*

*[Doc hides behind the alcove wall and goes silent. A beat, then the Tail walks past and into the alley.]*

*The Tail takes the bait and walks past. Little does he know this alley is one-way-only, and I've got him cornered.*

### Doc (sly)

Hold it, buster! It takes more than tracking to get the upper hand on me. How about telling me who you are, and why you've been following me?

### Doc (inner monologue)

*The Tail turns around to face me but sticks to the shadows of the alley. I can't get a good look at him, but from what I can see, he doesn't look like one of the Environmental Insults or Triggers I left behind at the Airway Epithelium. He's holding an eosinophil granule protein in his hand, tossing it up and down casually like he's ready to play ball. Did he just come from the crime scene?*

### Doc

You realize you're tampering with evidence?

### Tail (chuckling)

Plenty to go around. Those lungs won't miss a granule protein or two.

*[Doc pauses, choosing her words carefully]*

### Doc

I see you're familiar with the Airway Epithelium.

### Tail (gruff)

You could say that.

### Doc (gruffer)

That's good, cause I'm saying it. Now what are you saying?

**Tail**

I'm saying that Airway Epithelium may not be the "Pillar of the Community" people think.<sup>1</sup>

And those inflammatory cells? Well, they may not be the ones you're looking for, neither. This thing goes higher up. Straight to the top.<sup>2,3,4</sup>

**Doc (skeptically)**

That's a bold claim coming from someone with no name.

**Tail (matter of fact)**

Hey, take it or leave it, it's up to you.

**Doc**

Alright, tough guy, anything else you want to tell me?

**Tail**

That's all I got. For now. *[calling over shoulder]* See ya around, Doc.

*[The Tail tosses and catches the granule protein one more time and leaves. His footsteps retreat and echo down the alley]*

**Doc (inner monologue)**

*The Tail disappears into the shadows. Apparently there's another way out of this one-way alley after all, and he knew it. I get the feeling he wanted me to lead him here, which leaves me standing at the crossroads of Intrigued and Confused. I don't know whether to trust what I've just heard, but I have to believe there's something in it for this shady character. Why else would he offer up intel without wanting something in return?*

*Hang on a minute, though. He said this thing goes higher up.<sup>2,3,4</sup> I've heard something like that before...*

**Professor [in flashback]**

You also need to keep in mind that asthma patients have multiple and overlapping phenotypes or drivers of inflammation that can change over time.<sup>1,5</sup>

**Doc [in flashback]**

Overlapping phenotypes and changing drivers of inflammation. Good to know. That could make things tricky in this case if the cellular suspects keep changing.

**Professor [in flashback]**

Maybe, but... not if they answer to someone else...hmm...

*Hmm indeed. I've got to get back to Asthma HQ. Between the airway acting up back at the crime scene, the three suspects arriving for questioning soon, and this new Tail-shaped twist in the plot, there's no time to waste.*

*First stop: the top floor. Professor's pop quizzes will have to wait.*

*[Doc heads back to Asthma HQ. She enters the lobby and hurries toward the steps.]*

**Phil (distractedly)**

Welcome to Asthma HQ. Where can I direct— *[realizes]* oh hey, Doc! The elevator's—

**Doc (finishing his sentence)**

Elevator's still out, got it. I got a tight timeline, Phil! See you later!

*Phil (laughs)*

*[Doc continues toward the stairwell and begins climbing]*

**Doc (inner monologue; huffing and puffing)**

*That elevator's been out for a long time. Come to think of it, I'm not sure it's ever been "in," so to speak. Maybe Phil's teasing me and there never was an elevator in Asthma HQ. Deep thoughts to distract me on another long climb back up to the Professor's office.*

*[Doc reaches the top of the stairs and clomps into Professor's office]*

**Doc (out of breath)**

Hey Professor... I just came from—

**Professor**

The Airway Epithelium? Ohh Splendid. Did the Insults cause you any trouble?

**Doc (still out of breath)**

I held my own.... so it was fine... but—!

**Professor (charging ahead)**

What did you find inside? Any signs of an overactive immune response?

**Doc (slowly catching her breath)**

Yes... actually... on that note—

**Professor (still going)**

Oh, this just gets more interesting. I was doing some research while you were gone, and—

*[Doc finally catches her breath. With a big inhale, she interrupts the Professor during his train of thought.]*

**Doc**

You were right!

**Professor**

What?

**Doc**

Listen. Here's everything I know so far...

*Doc (inner monologue)*

*I fill him in on the details of my little stroll. A hyperresponsive airway, three suspects identified by the PI, and the Tail I picked up who tried to point me another way. Professor's hanging on every word.*

**Doc**

...That's when he said, "This thing goes higher up, straight to the top."<sup>2,3,4</sup> Which reminded me of what you said before I left. Do you think that's what's happening here?

*[Professor thinks for a moment.]*

**Professor**

Hmm. Could be... Maybe there *is* some method to this molecular madness after all. We still need to learn what the suspects know and don't know, but we can't assume anything at this point.

**Doc**

But at least two of our suspects – Eosinophil and IgE-Producing B Cell – left proteins and antibodies all over the crime scene. Seems safe to assume they had *something* to do with this severe exacerbation.

**Professor**

Yes, they most likely did. But keep in mind that the Eosinophil is inflammatory in nature and gets a little sloppy with its proteins everywhere it goes.<sup>3</sup> Likewise, B cells usually don't produce allergen-specific IgE. It's only after they're exposed to IL-4 and IL-13 that they switch to produce allergen-specific IgE. And the cells producing that IL4 and IL-13? Well, they in turn may be taking orders from somebody else higher up.<sup>2,8-10</sup> The question is: where, and to whom, does it all lead?

**Doc**

Well, I'll tell you where it leads me: right back down that *ridiculous* flight of stairs to meet our suspects. They've got information, and we need to know what they know.

**Professor**

Well, break a leg – just not while you're heading down those stairs...

**Doc**

One last thing, Professor: anything I should know about our third suspect, the Airway Smooth Muscle Cell?

**Professor**

Well, if it's coming from the scene of the crime, based on what you told me, it's likely pretty angry and hair-triggered already. This cell has a penchant for hyperreactivity and an eagerness to constrict the airway at the slightest taunts.<sup>2-4,11-13</sup> Getting information isn't going to be easy in its current state. But ask the right questions and even the most hyperreactive characters will cough up an important detail or two...

**Doc**

Like the way I cough every time I have to climb up here, maybe.

*[The door opens.]*

See ya next time, Professor.

**Professor**

Bye, bye!

*[The door closes.]*

*[Doc starts back down the stairs.]*

**Doc (inner monologue)**

*It's a long way down as usual, but the descent gives me a good chance to organize my thoughts. This case has thrown me a few enigmas wrapped in mysteries, but my team always puts me on the right track to tackle whatever comes my way.*

*Next on the agenda: some small talk with a few suspicious cells. A little determination and maybe a little more luck, and we'll pull together these loose threads and see what's hiding under the covers. I'm still cautious, but it's starting to feel like the pieces to some bigger puzzle on severe asthma may fall into place.*

*Time to see what our friends, the Eosinophil, IgE-Producing B Cell, and Airway Smooth Muscle Cell have to say on the subject.*

*I can't wait to meet them.*

**Announcer:**

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Join us next time for Part 4: The Suspects

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