The Q factor

By Lev Osherovich, Senior Writer

A study by **Active Biotech AB** has identified a cell-surface protein called S100A9 as the target of the company's lead molecule, a compound called laquinimod that is in Phase III testing for multiple sclerosis.¹ But because S100A9 is a known player in cancer, the new findings suggest a connection between autoimmune disease and tumor immunosuppression that may open up oncology as a potential new indication for either laquinimod or Active Biotech's next-generation quinoline-3-carboxamide compounds.

"These compounds have a very broad activity in models of autoimmune disease," said Tomas Leanderson, CEO of Active Biotech and professor of immunology at **Lund University**. "However, when people tried to look *in vitro* at their effects on immune cells, they drew a blank."

To find out how the compounds work, a team led by Leanderson synthesized laquinimod derivatives that were labeled with a radioactive probe. The group then searched for proteins from human immune cells that bound to the compounds, thus hitting upon S100 calcium binding protein A9 (S100A9; calgranulin B; MRP14).

The team went on to characterize how S100A9 mediates the binding of quinoline-3-carboxamide compounds (Q compounds) to immune cells. They found that Q compounds block the interaction between S100A9 and two early players in the process of inflammation: receptor for advanced glycation endproducts (RAGE) and toll-like receptor 4 (TLR4).

In a mouse model of autoimmunity, blocking S100A9 with either a Q compound or with mAbs against S100A9 prevented lipopolysaccharide-induced production of proinflammatory tumor necrosis factor- α (TNF- α) compared with that seen in mock-treated controls.

Altogether, the findings suggest that S100A9 links RAGE and TLR4 in a proinflammatory complex that can be disrupted by Q compounds. The results were published in *PLoS Biology*.

"We think that Q compounds are hitting an early step in immune activation, which could explain their biological activity in all the different autoimmune disease models," said Leanderson, alluding to previous studies.

"We suspect that there's a common step in the development of autoimmunity, but then depending on genetic factors you could get either MS, rheumatoid arthritis or another autoimmune disease."

Cancer connection?

In addition to suggesting S100A9 as a target in many autoimmune diseases, the *PLoS Biology* article hints at a connection between auto-

immunity and cancer, in which S100A9 is a known hallmark of the immunosuppressive myeloid-derived suppressor (MDS) cells that are frequently associated with tumor cells.²

Indeed, a pair of studies last year showed that a secreted form of S100A9 helps recruit MDS cells to solid tumors, in which they antagonize a protective immune response against the tumor cells.^{3,4}

Leanderson now suspects that MDS cells could be at work in both autoimmune diseases and cancers. In addition to their suppressive role in cancer, "MDS cells could be controlling self-targeting, and if so could be involved in autoimmunity," he told *SciBX*.

He added that Active Biotech is now testing its library of Q compounds to modulate S100A9 activity in prostate cancer models. The company already has a Q compound called TASQ in Phase II for prostate cancer, although it is uncertain whether TASQ acts via S100A9.

Moreover, it remains unclear whether S100A9 should be targeted in the same way in cancer and autoimmunity. The key question is what roles MDS cells play in the two diseases, said Suzanne Ostrand-Rosenberg, professor of biology at **The University of Maryland**.

"There's been a lot of recent work showing that MDS cells are prevalent in autoimmune disease," said Ostrand-Rosenberg. "This is puzzling because they're supposed to be suppressor cells, but clearly they're not in this setting. If MDS cells are implicated in autoimmunity, they really must be doing something quite different from what they do in cancer."

Dmitry Gabrilovich, professor of oncologic sciences and molecular medicine at the **University of South Florida**, said it's not certain whether the surface-associated form of S100A9 identified by Leanderson works the same way as the secreted S100A9 that has been linked to tumors.

He also noted that Q compounds might act on other proteins in addition to S100A9. Thus, Gabrilovich thinks the role of S100A9 in autoimmunity needs to be shored up with further *in vivo* experiments. "You would like to understand if you can reverse autoimmunity by showing a direct interaction between Q compounds and S100A9 *in vivo*," he said.

Gabrilovich noted that targeting inflammation to treat cancer hasn't yet paid off in the clinic, perhaps because of the relatively narrow window of time during which tumors can be controlled by the immune response. Earlier this decade, **Myriad Genetics Inc.**, **Encore Pharmaceuticals Inc.** and **Phytopharm plc** tried various NSAIDs for cancer indications without success.

Nonetheless, Gabrilovich said that Q compounds could improve the action of NSAIDs as potential cancer therapeutics, an idea that could be tested in preclinical cancer models.

"For cancer, Q compounds would need to be tried as an adjuvant to anti-inflammatory therapies," he noted.

According to Leanderson, a patent is pending for screening technology to identify S100A9 modulators. Compounds identified with this technology, including TASQ, are available for licensing from Active Biotech.

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REFERENCES

1. Björk, P. *et al. PLoS Biol.*; published online April 28, 2009; doi:10.1371/journal.pbio.1000097
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2. Fulmer, T. *SciBX* 1(38); doi:10.1038/scibx.2008.914
3. Cheng, P. *et al. J. Exp. Med.* **205**, 2235–2249 (2008)
4. Sinha, P. *et al. J. Immunol.* **181**, 4666–4675 (2008)

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