SciBX
Science-Business eXchange

Cancerous RAGE

By Michael J. Haas, Senior Writer

Mounting evidence has linked chronic inflammation and cancer, but the sheer number of pathways and molecules that could be involved has slowed the identification of the molecular mechanisms that may lead inflamed tissue to become cancerous. Researchers at the **German Cancer Research Center** and **University Hospital Heidelberg** have found a molecular mechanism by which chronic inflammation promotes skin tumors in mice. The findings indicate that receptor for advanced glycosylation end products and its ligands could be a target in epithelial and possibly other cancers.

In the Jan. 21 online edition of *The Journal of Experimental Medicine*, a research team led by Peter Angel reported that feedback between NF-κB and receptor for advanced glycosylation end products (RAGE)—a cycle that sustains inflammation—activated tumor-promoting functions of two RAGE ligands, S100A8 and S100A9, and led to skin tumor growth in mice.[1] Angel is head of the Division of Signal Transduction and Growth Control at the German Cancer Research Center (DKFZ).

> **"This paper provides a more direct molecular mechanism via RAGE and S100 proteins—instead of just 'hand-waving' around NF-κB signaling—to explain how inflammation leads to carcinogenesis."**
>
> ***—Noah Berkowitz, Synvista Therapeutics Inc.***

The results "describe a central, cell type–specific S100/RAGE axis that sustains inflammation, at least partly via NF-κB," said Christoffer Gebhardt, junior group leader at the Department of Dermatology at University Hospital Heidelberg and a coauthor on the paper. "I am convinced that blocking RAGE specifically is a promising new therapeutic approach for anticancer therapies."

RAGE is a transmembrane receptor expressed on a number of cell types, including epidermal keratinocytes, endothelial cells and innate immune cells such as neutrophils, macrophages and mast cells. It is classified as a scavenger receptor because of its clean-up function: binding advanced glycosylation end products (AGEs) that occur when excess blood sugars react with lipids or proteins. Both AGEs and RAGE are implicated in diseases where chronic inflammation plays a role, such as diabetes, neuropathy, atherosclerosis and Alzheimer's disease.

Interactions between RAGE and ligands like AGEs are thought to activate NF-κB, a known regulator of several genes involved in inflammation. RAGE itself is upregulated by NF-κB, thereby creating a positive feedback cycle that drives and sustains inflammation.

"We cannot define so far whether the S100/RAGE axis is active predominantly via NF-κB, AP-1 [adaptor-related protein complex 1] or perhaps other transcription factors," Gebhardt said. "We are currently addressing these questions by using *in vitro* and *in vivo* assays."

An earlier DKFZ team, also led by Angel, identified tumor-associated functions for S100A8 and S100A9.[2] Those results concurred with a study by researchers at **Columbia University**, **Osaka University School of Medicine** and **Kanazawa University School of Medicine** that linked RAGE to tumor growth but did not explore the mechanism by which this occurred.[3]

Companies contacted by *SciBX* agreed that the new *JEM* paper provided solid evidence that directly linked inflammation to carcinogenesis, but they also want to know more about what happens to the body when RAGE is blocked.

"It is an interesting article from a reputable group," said Noah Berkowitz, president and CEO of **Synvista Therapeutics Inc.** "It addresses a question brought up often in many biological pathways regarding the interface between inflammation and tumor development. The intersection of these two areas through RAGE is a new insight. This paper provides a more direct molecular mechanism via RAGE and S100 proteins—instead of just 'hand-waving' around NF-κB signaling—to explain how inflammation leads to carcinogenesis."

Nevertheless, Berkowitz said that certain questions need to be answered before RAGE could be pursued for cancer.

First, he noted that although the presence of RAGE is inflammatory in diseases such as diabetes and cancer, its role in other inflammatory diseases is less clear. For instance, studies at Columbia and the **CNR Institute of Clinical Physiology** suggest that RAGE is upregulated in rheumatoid arthritis (RA).[4,5] Yet a study at the **University of Göteborg** suggests that a deficiency in the nonmembrane, soluble isoform of RAGE (sRAGE) "might increase the propensity toward inflammation in patients with RA."[6]

"So RAGE is a double-edged sword," Berkowitz said. "Targeting it could be a useful approach to a disease like cancer, but it could create other problems."

In addition, he said, interfering with RAGE raises the issue of what becomes of AGEs that RAGE ordinarily binds.

"Synvista targets AGEs because we don't know where AGEs would accumulate and what they would do if we were to interfere with RAGE," Berkowitz said. "There is some evidence that they will bind to other scavenger receptors—like CD36—with untoward effects."

Eliminating AGEs directly causes no problems, he said, because they have no beneficial effects, whereas their continuing presence can serve as an inflammatory signal to receptors like RAGE.

"RAGE probably has many ligands other than AGEs and S100 proteins," he said. "Therefore, we should all be a bit cautious about inhibiting RAGE" without fully understanding all of the possible downstream effects.

Synvista's alagebrium breaks up AGEs so they can be metabolized. The compound is in Phase II testing to treat AGE-mediated myocardial stiffness that leads to heart dysfunction and to treat microalbuminuria and proteinuria resulting from inflammatory reactions to AGEs in type 1 diabetes. Results from both trials are expected in 2H09.

The compound's progression through the clinic has not been entirely smooth. In 2003, alagebrium failed in separate Phase II trials to treat systolic hypertension and diastolic heart failure. In 2005, Synvista (then Alteon Inc.) discontinued a Phase IIb trial of the compound to treat hypertension and a year later discontinued development to treat erectile dysfunction.

Christopher Reading, CSO of **Hollis-Eden Pharmaceuticals Inc.**, cautioned against putting too much emphasis on a single inflammation-related molecule—like RAGE—as a target for cancer.

"The *JEM* paper addresses one of a large number of processes that drive chronic inflammatory states," he said. "Once you trigger RAGE as part of the inflammation cascade, you involve NF-κB in an insidious, vicious cycle. The paper talks about this in cancer, but it happens in diabetes, too. Chronic inflammation states are involved in many diseases, and these states involve many common pathways. In one indication, targeting a molecule in one pathway could yield dramatic results," but this might not hold true in other indications.

As an example, Reading cited the resistance to anti–tumor necrosis factor-α treatment that can occur in RA. Resistance occurs over time in a fraction of subjects, he said, because there are many ways to maintain chronic inflammation: when one pathway is blocked, the body often finds another route.

Hollis-Eden's Triolex is an NF-κB inhibitor that is in a Phase I/II trial for type 2 diabetes. A Phase II trial is planned for this year.

Reading also noted that RAGE activates S100A8 and S100A9 in mice, but in humans RAGE activates S100A12. He said this raises the question of whether the findings by Angel's group would apply to human cancers.

Mice do not express S100A12—also called endogenous activator of RAGE—but mouse S100A8 and S100A9 proteins are structurally similar to human S100A12.

Gebhardt acknowledged that it has not yet been proven whether the mouse and human S100 proteins have similar functions. "But so far our *in vitro* experiments strongly suggest that human S100A8 and A9 bind to human RAGE," he said. "We have no data yet on binding of human S100A12 to RAGE."

Gebhardt said the research team is currently looking at whether the RAGE/S100 pathway is involved in other cancers, such as hepatocellular cancer, pancreatic cancer and melanoma.

"We have started work on translating our findings to human pathologies by analyzing tissue microarrays of various human cancers," he said. "I assume that in the near future, many other known signaling pathways in inflammation will be linked to certain functions in tumor development."

Gebhardt said the team has no plans to patent or license the findings. "At this stage, it would be more favorable to get patents for specific RAGE inhibitors," once such compounds have been developed, he said.

"We have initiated research to identify novel RAGE inhibitors," Gebhardt said. "We are looking forward to working together with the industry to assess them."

According to Reading, the process of translating discoveries about molecules like RAGE into practical therapies is part of a bigger picture.

"If you take all of this newfound information—that chronic inflammation is related to the genesis and progression of diseases like diabetes, cancer, hypertension and other cardiovascular diseases—you see that inflammation is related to aging," he said. "Disease by disease, paper by paper, this is culminating in the idea that stopping chronic inflammation could delay or prevent age-related diseases."

REFERENCES

1. Gebhardt, C. *et al. J. Exp. Med.*; published online Jan. 21, 2008; doi:10.1084/jem.20070679
   Contact: Peter Angel, Division of Signal Transduction and Growth Control, German Cancer Research Center, Heidelberg, Germany
   e-mail: p.angel@dkfz.de
2. Gebhardt, C. *et al. Oncogene* **21**, 4266–4276 (2002)
3. Taguchi, A. *et al. Nature* **405**, 354–360 (2000)
4. Basta, G. *et al. Circulation* **105**, 816–822 (2002)
5. Hofmann, M. *et al. Genes Immun.* **3**, 123–135 (2002)
6. Pullerits, R. *et al. Arthritis Res. Ther.* **7**, R817–R824 (2005)

COMPANIES AND RESEARCH INSTITUTIONS MENTIONED

CNR Institute of Clinical Physiology, Pisa, Italy
Columbia University, New York, N.Y.
German Cancer Research Center (DKFZ), Heidelberg, Germany
Hollis-Eden Pharmaceuticals Inc. (NASDAQ:HEPH), San Diego, Calif.
Kanazawa University School of Medicine, Kanazawa, Japan
Osaka University School of Medicine, Osaka, Japan
Synvista Therapeutics Inc. (AMEX:SYI), Montvale, N.J.
University Hospital Heidelberg, Heidelberg, Germany
University of Göteborg, Göteborg, Sweden