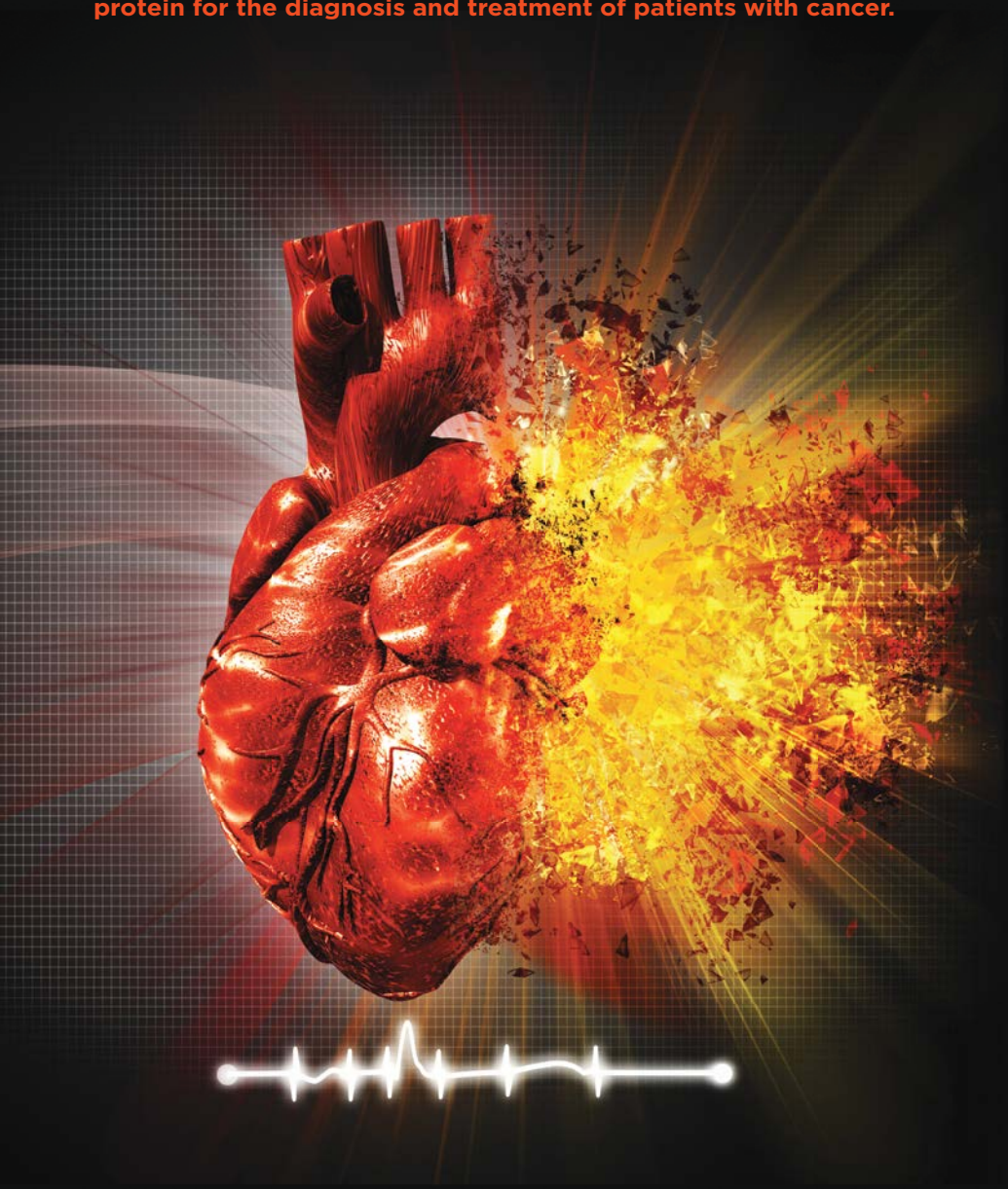
HMGB1 – a silent partner in cancer?

Many people in the life science and medical communities will never have heard of HMGB1 or, to give it its full title, high mobility group box 1 protein. Despite this, it is the most common nuclear protein after the histones – with around a million copies per cell – and plays a key role in the body's response to everything from trauma and infection to a stroke and heart attack. Dr Michael T Lotze, Professor of Surgery, Immunology and Bioengineering at the University of Pittsburgh School of Medicine, discusses the clinical interest in this remarkable protein for the diagnosis and treatment of patients with cancer.

Dr Michael T Lotze, University of Pittsburgh School of Medicine



Cell death in animals normally occurs via a highly regulated, carefully controlled process known as apoptosis. Designed to avoid the cell contents spilling out into the surrounding tissue and causing damage to neighboring cells, it results in the formation of carefully packaged apoptotic bodies which can be quickly and easily engulfed by phagocytic immune cells. In contrast to this, cancer cells do not undergo a programmed cell death, instead experiencing the unscheduled necrotic cell death normally associated with cellular trauma. Necrosis results in the loss of membrane integrity, leading to the release of the cellular carcass material into the extracellular space.

A clinical interest

One of the proteins released into tissues and the blood by the death of cancerous cells is HMGB1, a chromatin protein normally associated with the packaging of DNA in the cellular nucleus. In most animals, the presence of HMGB1 in the extracellular space is a critical 'alarm signal' – known as a damage-associated molecular pattern (DAMP) – triggering an inflammatory immune response to repair the damage. It also affects the surrounding cells directly by inducing autophagy, a 'self-preservation' mechanism which helps the intact cells to survive and repair themselves. Under normal circumstances, this would be

beneficial, but when the cell death is a result of chemotherapy, and the target cell that is being instructed to survive is a tumor cell, then you obviously have a problem. This not only promotes survival of the tumor cells, but it can also reduce their susceptibility to chemotherapy drugs. In addition, the localized presence of HMGB1 can suppress immunity, hindering natural antitumor responses such as T cell activation.

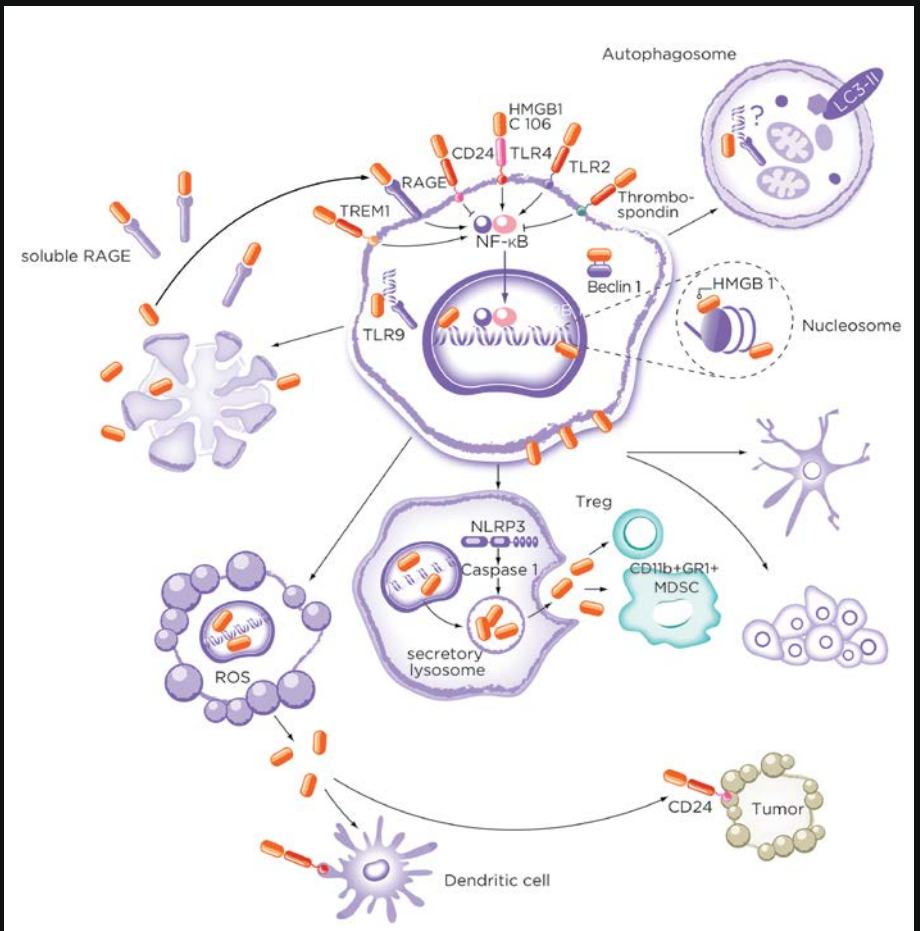
As a result, there is now significant interest in inhibiting HMGB1 in cancer patients – either directly, or up- or downstream – to suppress autophagy and the 'self-preservation' response in tumor cells. Early studies combining traditional chemotherapy with HMGB1-targeting immunotherapy have been remarkably successful in patients with pancreatic and kidney cancers, and additional trials are now being launched.

HMGB1 isn't only a problem at the tumor site either. Effective chemotherapy can lead to a significant and sustained rise in circulating HMGB1 – as well as other intracellular molecules, such as uric acid, potassium and nucleic acids – as the tumor responds to treatment. When released into the bloodstream, these molecules are filtered out by the kidneys, leading to a serious, and potentially fatal, form of kidney damage known as tumor lysis syndrome.

> "We know that HMGB1 is a critically important molecule, not just in cancer, but also in... many other biological processes."

Furthering research

One of the major challenges of HMGB1 is the availability of appropriate tools for research. Although many immunology and biochemistry groups around the world have attempted to develop ELISAs for the accurate quantification of HMGB1, it wasn't until the launch of IBL International's HMGB1 ELISA* that a reliable method was available. This assay system is intrinsically more effective than other approaches – nothing else comes close – and the company also offers a range of complimentary products, such as the Anti-HMGB1 Chicken IgY Neutralizing Polyclonal Antibody, making it faster and easier to conduct our investigations. We know that HMGB1 is a critically important molecule, not just in cancer, but also in autoimmunity, trauma, infection, myocardial infarction, stroke and many other biological processes that are not yet fully understood. It's becoming increasingly clear that it is important throughout medicine, and having the right tools available will help us to further our understanding and improve clinical approaches in the future.



HMGB1 is a key mediator for the immune system, signaling cellular stress, and can play a vital role as a biomarker for arthritis, stroke, cancer and sepsis.

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To find out more about IBL's HMGB1 ELISA kits, visit
www.tecan.com/immunoassays

To learn more about Dr Lotze's research, go to
www.immunology.pitt.edu/person/michael-lotze-md

The IBL HMGB1 ELISA Kit is CE marked for IVD use in Europe, but is for research use only in the USA.

*Developed by Shino-Test Corporation, Japan, in co-operation with Prof Dr Ikuro Maruyama of Kagoshima University, this product is exclusively distributed worldwide by IBL International, except in Japan, China (incl. Hong Kong) and Taiwan.