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## REPORT

### Turn Off Your Body's Aging "Switch"

By Morris Eagleton

In an important scientific advance, researchers have uncovered a biochemical "switch" that turns on many of the chronic diseases of aging.

The name of this newly identified "switch" is **HMGB1**, which stands for "**High Mobility Group Box-1**".

**HMGB1** turns on the release of chemical signals called **cytokines** that generate inflammation in your body.<sup>1</sup>

The more **chronic inflammation** you have, the more rapidly your body ages. The tragic consequence of higher levels of **inflammation** is the acceleration of chronic diseases that cause premature death and disability.<sup>1,2</sup>

Once scientists uncovered the switch that "turns on" chronic inflammation, they began looking for a safe and effective means of "turning off" that switch.

Researchers have found two natural ingredients that can directly control **HMGB1**, thus reducing the body's exposure to **chronic inflammation**, and ultimately protecting against inflammation-induced disorders.<sup>3,4</sup>



#### HOW HMGB1 TRIGGERS INFLAMMATION



The molecule **HMGB1** is responsible for initiating acute inflammation, which is a helpful reaction when your body is under attack by germs, or following an injury.<sup>5,6</sup> Unfortunately, when a cell is damaged, its contents of HMGB1 leak out, leading to *chronic* inflammation.<sup>5,6</sup>

When HMGB1 leaks out, it acts as a "danger signal" that triggers the release of chemical signaling molecules (called cytokines) that call in more white blood cells, which release still more cytokines, in a vicious cycle.<sup>1,5,6</sup>

At its worst, this activity can result in a massive, systemic release of cytokines that can shut down your body's entire system.<sup>7,8</sup> The deadly SARS outbreak of 2003 is an example of a *cytokine storm*, where it appears victims died as a result of the body's overreaction to the SARS

virus and not the virus itself.<sup>9-11</sup>

Fortunately, a true cytokine storm is rare. But the cumulative effects that result from HMGB1 slowly leaking from our aging cells are all too common.<sup>6</sup>

#### REVERSE CHRONIC INFLAMMATION!

Laboratory experiments have demonstrated that putting the brakes on **HMGB1** is a powerful means of slowing and reversing the

processes involved in inflammation.<sup>3,4</sup> In fact, scientists are examining the role of HMGB1 in the body and are using experimental models to begin making strides in the fight against inflammation in asthma, rheumatoid arthritis, diabetes, multiple sclerosis, and inflammatory bowel diseases.<sup>12-20</sup>

Big Pharma is frantically working to create treatments that target HMGB1, but at this point no anti-HMGB1 drug is anywhere near market-ready.<sup>21</sup>

The good news is that two natural substances, **mung bean** and an extract from **green tea**, have been found to suppress HMGB1—providing anti-inflammatory power.<sup>3,4</sup> And best of all, they're available in an oral form.

## DUAL PROTECTION AGAINST CHRONIC INFLAMMATION

**Mung bean** and **green tea** extract combat inflammation by interfering at several different points in the cascade of events that leads to HMGB1 release from stressed or damaged cells.<sup>3,4,22-25</sup> Most of today's anti-inflammatory drugs only work on a single target point of inflammation.<sup>26</sup>

Nearly all of the mung bean's HMGB1-lowering action is found in the **seed coat** of the bean.<sup>4</sup> When fed to rats before or after exposure to heat stress, **mung bean seed coat** extract reduced blood markers of excessive oxidant stress, while also strengthening the body's natural antioxidant defense system.<sup>27</sup>

When cells are exposed to bacterial toxins, **EGCG** (the major beneficial component in green tea) reduces HMGB1 release from cells in direct proportion to the dose.<sup>3</sup> Importantly, EGCG has been found to drive down HMGB1 release even when given **2 to 6** hours *after* exposure of cells to the toxin.<sup>3,24</sup>

## DRAMATIC STUDIES SHOW INCREASED LIFE SPAN!

Three recent studies demonstrate the dramatic life-saving ability of **mung bean seed coat** and **EGCG** from green tea leaf.<sup>3,4,24</sup>

They all involve **sepsis**, a condition involving HMGB1 that kills hundreds of thousands of Americans every year in hospital intensive care units, despite modern antibiotics and life-saving technology.<sup>28</sup> (Sepsis is an illness in which the body has a severe, systemic inflammatory response to infection.<sup>22</sup>)

In sepsis, HMGB1 triggers an outpouring of **cytokines**. It is this resulting inflammation—and *not the infecting germ*—that ultimately kills the patient.<sup>1,29,30</sup> Once those cytokines are on the loose, it's typically too late to fight back with anti-cytokine therapies.<sup>31-33</sup>



With this in mind, researchers chose to study **mung bean seed coat** extract and **EGCG** from green tea leaf extract, based on their known anti-HMGB1 activities.

The researchers first induced sepsis in laboratory mice, dooming them to almost certain death without intervention.<sup>3,4,24</sup>

In one experiment, the mice orally received either EGCG, found in green tea, or a saline control at **24, 48, and 72** hours *after* the induction of sepsis.<sup>24</sup> By **day 2**, **44%** of the **control** mice survived, while **89%** of the EGCG group remained alive. By **day 5**, only **16%** of the control group survived, while **44%** of the EGCG group survived for the duration of the study.<sup>24</sup>

Next, the researchers studied **mung bean seed coat extract**.<sup>4</sup> Using the same experimental design as in the previous study, the mice were given the extract or a saline control the day after induction of sepsis. By **day 2**, only **53%** of control mice survived, while **82%** of those mice supplemented with mung bean coat remained alive. By **day 4**, only **29%** of the control group survived, while **70%** of the mung bean group remained alive.<sup>4</sup>

It's impossible to overstate the significance of these results. For the first time ever, septic shock was significantly prevented, and animals were rescued from an otherwise likely death, **using a simple, natural, oral treatment**. The secret to these results was the sharp drop in HMGB1 levels induced by both EGCG and mung bean seed coat extract.<sup>3,4,24</sup>

## SLOW DOWN THE AGING PROCESS

These studies demonstrate just how powerfully these two natural ingredients work even in the direst of situations. Fortunately, most of us will never have to deal with sepsis or the out-of-control inflammation that it can produce. But all of us face the dangers imposed by **chronic inflammation**.

Both **EGCG** and **mung bean seed coat** extract can powerfully suppress HMGB1, reducing levels of total-body chronic inflammation.<sup>3,4,24</sup>

Reduced chronic inflammation can translate to longer and substantially healthier lives. In this way, mung bean seed coat extract and EGCG can slow down damaging aging processes and potentially prolong your life.

### SUMMARY

Chronic inflammation accelerates aging and is an underlying factor in many of the diseases associated with aging.<sup>1,2,34</sup> Scientists have discovered a way to inhibit **HMGB1**, the molecule that “turns on” the release of **inflammatory cytokines**.<sup>3-6,24</sup>

**Mung beans** and **green tea** have been in use for thousands of years in traditional Chinese medicine.<sup>3,4</sup> They both contain powerful substances that inhibit **HMGB1**. Lab studies have proven that these substances are highly effective at “turning off” the HMGB1 switch that induces chronic inflammation.<sup>3,4,24</sup>

**Mung bean seed coat extract** and **EGCG** are available in oral form, making their combined **HMGB1-blocking** effect convenient to take by mouth.

If you have any questions on the scientific content of this article, please call a **Life Extension**<sup>®</sup> Health Advisor at 1-866-864-3027.

### REFERENCES

1. Nogueira-Machado JA, de Oliveira Volpe CM. HMGB-1 as a target for inflammation controlling. *Recent Pat Endocr Metab Immune Drug Discov*. 2012 Sep;6(3):201-9.
2. Strzelecka M, Bzowska M, Koziel J, et al. Anti-inflammatory effects of extracts from some traditional Mediterranean diet plants. *J Physiol Pharmacol*. 2005 Mar;56 Suppl 1:139-56.
3. Li W, Ashok M, Li J, Yang H, Sama AE, Wang H. A major ingredient of green tea rescues mice from lethal sepsis partly by inhibiting HMGB1. *PLoS One*. 2007;2(11):e1153.
4. Zhu S, Li W, Li J, Jundoria A, Sama AE, Wang H. It is not just folklore: The aqueous extract of mung bean coat is protective against sepsis. *Evid Based Complement Alternat Med*. 2012;2012:498467.
5. Zhu S, Li W, Ward MF, Sama AE, Wang H. High mobility group box 1 protein as a potential drug target for infection- and injury-elicited inflammation. *Inflamm Allergy Drug Targets*. 2010 Mar;9(1):60-72.
6. Klune JR, Dhupar R, Cardinal J, Billiar TR, Tsung A. HMGB1: endogenous danger signaling. *Mol Med*. 2008 Jul-Aug;14(7-8):476-84.
7. Kruttgen A, Rose-John S. Interleukin-6 in sepsis and capillary leakage syndrome. *J Interferon Cytokine Res*. 2012 Feb;32(2):60-5.
8. Ye C, Choi JG, Abraham S, et al. Human macrophage and dendritic cell-specific silencing of high-mobility group protein B1 ameliorates sepsis in a humanized mouse model. *Proc Natl Acad Sci U S A*. 2012 Dec 18;109(51):21052-7.
9. Huang KJ, Su IJ, Theron M, et al. An interferon-gamma-related cytokine storm in SARS patients. *J Med Virol*. 2005 Feb;75(2):185-94.
10. Li Y, Chen M, Cao H, Zhu Y, Zheng J, Zhou H. Extraordinary GU-rich single-strand RNA identified from SARS coronavirus contributes an excessive innate immune response. *Microbes Infect*. 2013 Feb;15(2):88-95.
11. Theron M, Huang KJ, Chen YW, Liu CC, Lei HY. A probable role for IFN-gamma in the development of a lung immunopathology in SARS. *Cytokine*. 2005 Oct 7;32(1):30-8.
12. Shim EJ, Chun E, Lee HS, et al. The role of high-mobility group box-1 (HMGB1) in the pathogenesis of asthma. *Clin Exp Allergy*. 2012 Jun;42(6):958-65.
13. Andersson U, Tracey KJ. HMGB1 as a mediator of necrosis-induced inflammation and a therapeutic target in arthritis. *Rheum Dis Clin North Am*. 2004 Aug;30(3):627-37, xi.
14. Andersson U, Harris HE. The role of HMGB1 in the pathogenesis of rheumatic disease. *Biochim Biophys Acta*. 2010 Jan-Feb;1799(1-2):141-8.
15. Uzawa A, Mori M, Taniguchi J, Masuda S, Muto M, Kuwabara S. Anti-high mobility group box 1 monoclonal antibody ameliorates experimental autoimmune encephalomyelitis. *Clin Exp Immunol*. 2013 Apr;172(1):37-43.

16. Robinson AP, Caldis MW, Harp CT, Goings GE, Miller SD. High-mobility group box 1 protein (HMGB1) neutralization ameliorates experimental autoimmune encephalomyelitis. *J Autoimmun.* 2013 Mar 17.
17. Maeda S, Hikiba Y, Shibata W, et al. Essential roles of high-mobility group box 1 in the development of murine colitis and colitis-associated cancer. *Biochem Biophys Res Commun.* 2007 Aug 24;360(2):394-400.
18. Andersson UG, Tracey KJ. HMGB1, a pro-inflammatory cytokine of clinical interest: introduction. *J Intern Med.* 2004 Mar;255(3):318-9.
19. Han J, Zhong J, Wei W, et al. Extracellular high-mobility group box 1 acts as an innate immune mediator to enhance autoimmune progression and diabetes onset in NOD mice. *Diabetes.* 2008 Aug;57(8):2118-27.
20. Yang H, Hreggvidsdottir HS, Palmblad K, et al. A critical cysteine is required for HMGB1 binding to Toll-like receptor 4 and activation of macrophage cytokine release. *Proc Natl Acad Sci U S A.* 2010 Jun 29;107(26):11942-7.
21. Cozzani E, Burlando M, Parodi A. Detection of antibodies to anti-TNF agents in psoriatic patients: a preliminary study. *G Ital Dermatol Venereol.* 2013 Apr;148(2):171-4.
22. Chen X, Li W, Wang H. More tea for septic patients?--Green tea may reduce endotoxin-induced release of high mobility group box 1 and other pro-inflammatory cytokines. *Med Hypotheses.* 2006;66(3):660-3.
23. Kuang X, Huang Y, Gu HF, et al. Effects of intrathecal epigallocatechin gallate, an inhibitor of Toll-like receptor 4, on chronic neuropathic pain in rats. *Eur J Pharmacol.* 2012 Feb 15;676(1-3):51-6.
24. Li W, Zhu S, Li J, et al. EGCG stimulates autophagy and reduces cytoplasmic HMGB1 levels in endotoxin-stimulated macrophages. *Biochem Pharmacol.* 2011 May 1;81(9):1152-63.
25. Saiwichai T, Sangalangarn V, Kawahara K, et al. Green tea extract supplement inhibition of HMGB1 release in rats exposed to cigarette smoke. *Southeast Asian J Trop Med Public Health.* 2010 Jan;41(1):250-8.
26. Burnett BP, Levy RM. 5-Lipoxygenase metabolic contributions to NSAID-induced organ toxicity. *Adv Ther.* 2012 Feb;29(2):79-98.
27. Cao D, Li H, Yi J, et al. Antioxidant properties of the mung bean flavonoids on alleviating heat stress. *PLoS One.* 2011;6(6):e21071.
28. Cai B, Deitch EA, Ulloa L. Novel insights for systemic inflammation in sepsis and hemorrhage. *Mediators Inflamm.* 2010;2010:642462.
29. Naglova H, Bucova M. HMGB1 and its physiological and pathological roles. *Bratisl Lek Listy.* 2012;113(3):163-71.
30. Available at: <http://www.mayoclinic.com/health/sepsis/DS01004>. Accessed September 10, 2013.
31. Khalil AA, Hall JC, Aziz FA, Price P. Tumour necrosis factor: implications for surgical patients. *ANZ J Surg.* 2006 Nov;76(11):1010-6.
32. Qiu P, Cui X, Barochia A, Li Y, Natanson C, Eichacker PQ. The evolving experience with therapeutic TNF inhibition in sepsis: considering the potential influence of risk of death. *Expert Opin Investig Drugs.* 2011 Nov;20(11):1555-64.
33. Sama AE, D'Amore J, Ward MF, Chen G, Wang H. Bench to bedside: HMGB1-a novel proinflammatory cytokine and potential therapeutic target for septic patients in the emergency department. *Acad Emerg Med.* 2004 Aug;11(8):867-73.
34. Howcroft TK, Campisi J, Louis GB, et al. The role of inflammation in age-related disease. *Aging (Albany NY).* 2013 Jan;5(1):84-93.

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