Renowned medical researcher Professor Istvan Boldogh gives an insight into his work towards better understanding the role of oxidative DNA damage and repair in human health.

How would you describe the current aims of your lab?

Our overarching goal is to elucidate the fundamental mechanisms by which the repair of oxidatively damaged DNA is implicated in inflammatory processes – symptoms that are common to asthma and chronic pulmonary lung diseases. These are complex diseases involving immunological, genetic and epigenetic mechanisms, and the associated clinical symptoms are exacerbated by environmental factors, as well as factors generated intrinsically by things like stress.

Common to all asthma phenotypes and chronic obstructive pulmonary lung diseases is an increased oxidative state, leading to supraphysiological levels of oxidatively-modified macromolecules including DNA. In DNA the most frequent example of damage is 8-oxoguanine, which is repaired via 8-oxoguanine DNA glycosylase-1 (OGG1)-initiated DNA base excision repair. Our immediate goal is to establish that this repair process is aetiologically coupled with the expression of chemokines, cytokines and growth factors, and long-term transcriptional reprogramming in the epithelium fuelling chronic inflammation. We are determined to identify medical solutions to stop inflammation in asthma and other pulmonary diseases – as no such solutions currently exist.

What first inspired you to work in this area of research, and what have been your proudest achievements to date?

Initially, I was working on free radical biology, investigating the mechanisms of reactive oxygen species (ROS) generation by mitochondria and oxido-reductases, as well as ROS signalling as this plays a role in lung inflammatory processes. However, experimental data indicated an apparent contradiction between the specificity of ROS that would be required for signalling and their indiscriminate damaging effect on biomolecules due to their extremely reactive nature. Thus, I proposed that signalling by various ROS must be ‘funnelled’ into a common molecule to generate a specific cellular response. As DNA integrity is key to life, DNA damage-induced signalling was one of the possible explanations. I was close, but I soon recognised that the signalling would have to be more specific than could be achieved through abundant oxidative DNA damage. One of the most significant achievements was identifying the OGG1:8-oxoguanine complex functioning as a guanine nucleotide exchange factor. From this point, it was easy.

You are Director of the Tissue Culture Core Laboratory at the University of Texas Medical Branch. Can you outline some of the other research projects you are overseeing in this lab?

The Core provides services to investigators in the Departments of Biochemistry and Molecular Biology, Pharmacology and Toxicology, Microbiology and Immunology and in Centers such as the Sealy Center for Molecular Medicine, Environmental Toxicology – as well as clinical departments university-wide. Directing this facility gives me the opportunity to work with outstanding investigators funded by the National Institutes of Health (NIH), and their colleagues, including scientists, postdoctoral fellows and students. A particular strength of this facility is that it serves as an integrating umbrella to foster collaborative arrangements across departmental boundaries and encourage productive interactions between basic and translational sciences. It is a great pleasure for me to discuss science with our investigators and share knowledge, successes and issues we are facing in research laboratories.

As 8-oxoguanine repair occurs in every cell in the body, it has far-reaching consequences; has this led you to forge collaborations with medical researchers in different disciplines?

Certainly – and, importantly, I would not have been able to achieve the advances I have without leading US and international researchers in DNA repair, signal transduction, tumour biology, neuroscience, ageing and allergy and immunology.

In light of the environmental pollutants/chemicals that contribute to increased levels of cellular ROS, are there any public health measures that you would like to see implemented to decrease exposure to such substances?

Being an investigator funded by the National Institute of Environmental Health and Sciences (NIEHS) I am familiar with recent efforts taken by that organisation along with the Environmental Protection Agency (EPA) in regard to public health measures. NIEHS and EPA partnerships with local environmental arms of public health departments are secure and improve our living environment. These partnerships have already established measures such as networking between community organisations and environmental scientists to match site-specific exposure concerns with research; strategic scientific, educational and advocacy planning in response to emerging environmental health issues; and effective environmental public health and outreach strategies to enhance community knowledge and inform them about policies. Therefore, we are in good hands in the US.
Sending mixed signals

A dedicated team of researchers at the University of Texas is investigating the possibility that cellular signals generated by a complex formed by a DNA repair enzyme and its repair product could play a role in pathologies such as inflammation, and diseases that result from it.

WHEN IT COMES to dangerous chemical elements, few people would think to highlight oxygen. Indeed, in its molecular form oxygen is fairly stable and innocuous – but the same cannot be said for certain reactive species of this element that can arise within the human body. Reactive oxygen species (ROS) are natural by-products of oxygen metabolism, and are created when molecular oxygen is incompletely reduced. As their name implies, these chemicals are unstable, and this is one of the reasons they pose a danger to the human health when in excess.

Because ROS are capable of reacting so readily, they can cause damage to many integral cellular components. They oxidise both lipids and amino acids in proteins; oxidatively inactivate enzymes and their cofactors; and can often react with and damage DNA. It has been hypothesised that gradual cumulative damage from ROS is the root cause of many diseases and ageing processes, and it is for these reasons that much attention has been focused in recent years on the mechanism by which ROS and oxidatively modified molecules generate both beneficial and potentially harmful cell activation signals.

A CORRUPTED COMPLEX

When DNA is attacked by ROS, the most common casualty is the base guanine, which has the lowest oxidation potential among DNA bases. Most frequently, the reaction with guanine results in 8-oxoguanine, a modified DNA base that is silent – that is, it does not cause structural change in DNA. This new base is often not recognised by RNA and DNA polymerases, but still pairs with adenine and creates mutations when it is read. To maintain DNA fidelity, cells have their own enzyme specifically for the task of dealing with 8-oxoguanine in DNA molecules: 8-oxoguanine DNA glycosylase-1 (OGG1). In a process known as OGG1-initiated DNA base excision repair, 8-oxoguanine is cut out of the genetic sequence by the OGG1 enzyme and transported into the cytoplasm, where it is dumped. For one team of scientists at the University of Texas Medical Branch, the story does not end there. Istvan Boldogh is a professor in the University’s Department of Microbiology and Immunology, and his research over the last few years has pursued the impact of 8-oxoguanine after it has been removed from DNA. His team’s work has suggested that this misbegotten molecule goes on to join with partners in the cytoplasm and subsequently affects signalling processes, especially those responsible for inflammation. If this is the case, then Boldogh’s studies may have practical applications in the context of many conditions that benefit or adversely affect human health.

THE MASTER SWITCH

For a long time, scientists considered 8-oxoguanine to be nothing more than an unreactive product of oxidative stress. What is more, because of the prevalence of damaging oxidative processes, this discovery has even greater significance than is immediately apparent. “OGG1-initiated DNA base excision repair occurs in every cell and goes on throughout our whole lives, and we have a considerable amount of data to show that its product, the OGG1:8-oxoguanine complex, is therefore a master regulator of many cellular signalling processes,” Boldogh explains. This prolific molecule can trigger various responses at the cellular level, from cell proliferation and differentiation to senescence and apoptosis. In particular, it is likely to have a hand in the activation of pro-inflammatory networks such as those involved in inflammatory networks such as those involved in the root cause of many diseases and ageing processes.

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in any number of chronic conditions, including asthma and other pulmonary lung diseases, arthritis and Alzheimer’s disease.

**EXPERIMENTAL EXAMINATION**

Because the burden of asthma and chronic obstructive pulmonary lung disease is particularly high in the US, affecting more than one fifth of all Americans, the Texan scientists chose to focus their studies on the impact of the OGG1:8-oxoguanine complex on the lungs in particular. Using a combination of *in vivo* and *in vitro* studies alongside state-of-the-art biological approaches, Boldogh and his group have been able to uncover a number of surprising conclusions about the signalling operations of OGG1:8-oxoguanine. Perhaps most importantly, they found that curtailing DNA repair by silencing OGG1 with RNA interference prevented epithelial cells in the airways from producing a robust inflammatory response to allogenic stimuli.

Depletion of OGG1 or RHOA, similarly, was found through experiments with murine models to prevent the structural changes usually found in the lungs of patients with asthma or chronic obstructive pulmonary lung disease. Finally, the silencing of OGG1 was shown to block the accelerated ageing of cells both in culture and in animal models. At every turn, it seems that aberrant signalling from this previously unknown molecular mechanism is associated with the same symptoms that characterise inflammation in atopic, non-atopic and severe asthma. Further elucidating the basis of these processes will therefore potentially yield important answers for healthcare in this area – and likely others as well.

An example of this can be readily seen within the group’s own studies, particularly in a further discovery that has immediate practical implications. Boldogh and his colleagues found that administering 8-oxoguanine to OGG1-expressing cells, or to experimental animals generally, induced a strong innate immune response evidenced by chemo- and cyto-kine expression and the gathering of neutrophils and macrophages at the inoculation site. This local immune response proved to be such an effective way of boosting the immune response against antigens that the team patented the use of 8-oxoguanine as an adjuvant therapy.

**LOOKING AHEAD**

Boldogh describes his lab’s research programme as prosperous, and indeed the truth of this assessment is exemplified not only by the worthwhile discoveries of his team, but also by its prolific publication record and funding success. “I am passionate about biomedical research, and this passion will keep me going, as well as my continuing about biomedical research, and this passion will keep me going, as well as my continuing

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