

Healthcare industry BW

Stress and molecular defence mechanisms

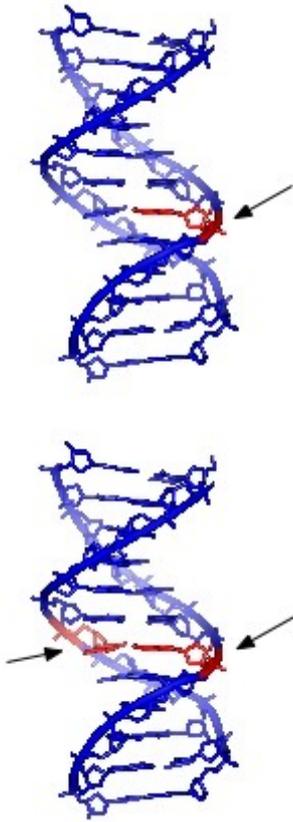
Organisms can experience stress from exposure to bacteria and pathogenic fungi; in fact, stress can arise from exposure to any type of environmental influence. As they have evolved, biological cells have developed numerous molecular mechanisms that enable them to survive even in inhospitable conditions. What kind of effects do abiotic stress factors have on plants and human beings? How do cells protect themselves? Are researchers able to increase the tolerance of plants and humans to stress in order to increase crop yields in developing countries or combat diseases such as Parkinson's and cancer? State-of-the art molecular biology methods provide stress researchers with new ideas, and Baden-Württemberg scientists are at the forefront of such research.

Too much sunlight, too low or too high a temperature, elevated dosages of salt, heavy metals and other chemicals are all stress factors. And even the air that we breathe is a stress factor as it contains oxygen radicals that can react with and destroy healthy cells. Such abiotic stress factors can have many harmful effects on the cellular metabolism: they can induce DNA mutations, cause proteins to lose their functional form and interfere with signalling cascades. The metabolism can be damaged to a degree that entire tissues and organs cease functioning. Abiotic stress can be fatal for cells and organisms. It is particularly threatening to plants as they are unable to run away or hide when inhospitable conditions arise. Researchers around the world are investigating the effects of stress on plants for the simple reason that crop yield is closely related to the plants' performance when exposed to stress. Human beings also experience health problems that are closely related to the exposure to abiotic stress factors.

Two principle protection systems

Oxidative stress is an excellent example for illustrating the harmful effects of abiotic stress on an organism's genome. Reactive oxygen species, i.e. molecules with unpaired electrons, are constantly being formed in the cells as a consequence of detoxification processes in the liver or exposure to ionising radiation. These free radicals react with and alter the molecular structures of cells. This can lead to DNA damage that can cause entire genes to lose their function. Cellular lipids and proteins can also be affected. It is assumed that such processes lead to the rapid ageing of cells. Oxidative stress has also been found to be related to neurodegenerative diseases that develop as a consequence of damage occurring to important proteins in the dopaminergic neurons in a brain area known as substantia nigra. Parkinson's disease, for example, is caused by the death of dopaminergic neurons in this particular brain structure.

To a certain degree, reactive oxygen species are normal metabolic products of cells; they are mostly



Oxidative stress can lead to DNA breaks.

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formed within the mitochondria of a cell. But the dose makes the poison. Cells have two different protection systems that help them to maintain a physiological equilibrium of free radicals. On the one hand, cells possess molecules (e.g. glutathione) that are able to capture free electrons before they are able to do any harm. On the other hand, cells are able to specifically degrade damaged proteins and repair DNA damage. The latter includes mechanisms that are able to repair mutations of individual genes as well as of entire sections of chromosomes. If cells are unable to repair such damage (for example due to the fact that the mutation rate is higher than the repair rate or the repair mechanisms no longer work due to mutations of the genes involved), they are then able to halt cell division and carry out the repairs needed to prevent DNA damage being transferred to the daughter cells. If this is also no longer possible, the cells are likely to undergo apoptosis, i.e. programmed cell death.

Chaperones and exposure to high temperatures

Living organisms on planet earth learned very early on how to combat environmental upsets. Even such simple organisms as bacteria possess so-called heat shock proteins. High temperatures can alter the structure of proteins, a phenomenon that is referred to as protein denaturation. This phenomenon also occurs when eggs are fried or boiled and the egg white solidifies. Heat causes molecular bonds in a protein to dissolve and new bonds to form, which can affect the three-dimensional structure of proteins and hence their biological function. In 1962, researchers working on the fruit fly *Drosophila melanogaster* discovered that heat leads to chromosome puffing. The researchers found that *Drosophila* cells increase the expression of certain proteins upon exposure to heat (the puffed-up regions are sites with higher expression rates, i.e. sites where RNA is synthesised). These proteins, which were later named heat shock proteins (HSP), recognise wrongly folded proteins and help them to fold back into their proper form. They are found in all organisms, including

bacteria, plants and humans.



The photo shows the light blue surface of a volcanic lake surrounded by an orange ring.
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It is now known that the elevated expression of heat shock proteins can be induced by many stress factors (e.g., toxins, hunger, UV light, salt, reactive oxygen species, drought). Bacterial species that live in volcanic craters or hot springs would not be able to survive without heat shock molecules. In the 1980s, it was found that lower quantities of HSPs were formed under normal conditions. HSPs have also been found to act as molecular chaperones that control the proper folding of proteins. Cancer cells have higher quantities of heat shock proteins that promote the survival of tumours. They protect the tumour against the effect of stress that occurs as a consequence of rapid cell division (which is typical for cancer cells) and as a consequence of chemo- and radiation therapy. HSP inhibitors (e.g., 17-AAG, HSP90 inhibitor) are used in cancer therapy.

Cancer, harvest loss and complex stress networks

It goes without saying that stress that induces DNA damage can lead to cancer. Mutated genes that regulate DNA repair, the degradation of defective proteins, control the cell cycle or apoptosis, can make cells go off the straight and narrow and encourage the development of tumours. Damage to DNA, proteins and lipids can also occur in plants, where it can prevent or at least delay their growth. This is why resistance to stress has become a key topic in plant biotechnology where researchers seek to introduce stress tolerance genes into agricultural crops or breed particularly resistant genotypes (one such effort is the attempt to transfer the stress tolerance gene of wild vines to cultivated vines). Scientists are confronted with another problem in bacteria research: many processes in industry or hospitals are very susceptible to microorganisms (for example bacteria that occur in pipes and cannulas that need to remain sterile). Microorganisms are very resistant to

disinfectants and detergents. How can the mechanisms that protect them against stress be targeted?

Using systems biology methods, modern research has developed efficient ways to elucidate the complex signalling networks that play a role in the recognition, processing and defence of stress. In addition, comparative genomics also provides insights into these networks: effective methods have been found that are used to achieve an in-depth understanding of the evolution of numerous stress tolerance genes in cells, researchers are increasingly able to identify conserved structures that play a role in stress tolerance, thus enabling them to decipher essential stress tolerance mechanisms. Furthermore, major insights arise from the comparison of results obtained from different model animals. For example, results gained in the field of ageing research involving the threadworm *Caenorhabditis elegans* can and need to be compared with results from other species and from human cell lines in order to enable the more effective transfer of results to the situation in humans. Stress will remain an important topic in the future because there is no escape from environmental influences. In addition, today's lifestyle is increasingly creating the stress we as humans are exposed to: the effects of particulate matter that comes from the toner used in printers, asbestos, mobile phone radiation and exhaust fumes will become a greater threat in the future. Baden-Württemberg is an excellent location for stress research at all levels. This dossier provides insights into the Baden-Württemberg laboratories that are working on this topic.

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