Glaucoma may soon be treatable by harnessing self-reactive immune cells to contain neuronal damage, according to a leading neurobiologist.

According to Professor Michal Schwartz PhD, autoimmunity may account for how the body can protect itself against some forms of glaucoma and a number of other neurodegenerative disorders. In other words, glaucoma may be exacerbated by a systemic malfunction in the immune system. Dr Schwartz, who holds the Maurice and Ilse Katz Professorial Chair in Neuromunology at the Department of Neurobiology at the Weizmann Institute, in Israel, reported her most recent findings to the 7th Scientific Meeting of the Association for Ocular Pharmacology and Therapeutics held earlier this year in Catania, Sicily.

Her findings - which she presented to approximately 200 delegates from the US, EU and Japan - represent a new view of autoimmunity. Although seemingly counter-intuitive, Dr Schwartz’s theory is based on a large volume of data that support the concept that promotion of autoimmunity in a controlled manner might lead to a promising therapeutic approach to glaucoma and other neurodegenerative disorders.

**Using protective autoimmunity to treat disease**

The immune system plays a pivotal role in neurodegenerative diseases. In cases of glaucoma, it has been documented that retinal ganglion cell loss can occur even when ophthalmologists successfully lower the IOP. Consequently, it is clear that a successful therapeutic approach to treating glaucoma may require a means to provide neuronal cell protection in addition to lowering IOP.

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**Autoimmune research based on theory of ‘What doesn’t kill us makes us stronger’**

A common principle of Dr Michal Schwartz’s “protective autoimmunity” is “What doesn’t kill us makes us stronger.” Just as properly controlled apoptosis is not only desirable but necessary for a healthy body, Dr Schwartz argues that a little autoimmunity, in the right place and at the right time, may be an important and beneficial physiological process.

So what is “protective autoimmunity”? We should distinguish between “autoimmunity” and “autoimmune disease”. When one thinks of autoimmune disease, it all sounds rather negative: multiple sclerosis, rheumatoid arthritis, type I diabetes, cardiomyopathy, Guillain-Barré syndrome, Crohn's disease, lupus erythematosus, alopecia, psoriasis - all clearly disordered conditions which we need to avoid at all costs. In such diseases the immune levels are over-reacting and thus the immune response that recognises itself is beyond the ability of the body to tolerate and thus is causing tissue loss and deterioration.

However, at the 7th Scientific Meeting of the Association for Ocular Pharmacology and Therapeutics held earlier this year in Catania, Sicily, Dr Schwartz noted that while autoimmune diseases are a problem, “autoimmunity” is not.

**What doesn’t kill us makes us stronger**: immune cells react to self antigens, such as immune B-cells and T-cells represent a counter-intuitive, Dr Schwartz’s theory is based on a large volume of data that support the concept that promotion of autoimmunity in a controlled manner might lead to a promising therapeutic approach to glaucoma and other neurodegenerative disorders.

*Autoimmunity is a physiological pivotal response of the body, and only when it is not well controlled does it cause a disease. Autoimmune disease is an outcome of malfunctioning autoimmunity.*

This is, of course, reminiscent of apoptosis - the physiological process of cell death that, if not well controlled, leads to disorders such as cancer and neurodegenerative disease.

Dr Schwartz has developed a rational concept as to how autoimmunity, like apoptosis, plays a critical role in maintaining a healthy body. Like apoptosis, autoimmunity needs to be tightly controlled but in the right circumstances - a little dose of autoimmunity - can turn out to be an important protective measure for the body and so, the concept of “protective autoimmunity” recognises the potential positive elements of self-reactive immune cells that fight off internal enemies, unlike immunity that fights off invading microbes or viruses. Again, like apoptosis, the principle of “protective autoimmunity” makes perfect sense when one considers the good of the organism rather than the good of a single cell.

Dr Schwartz’s ideas of protective autoimmunity, if correct, represents a further fundamental aspect of nature that in time may revolutionise our understanding of disease, not unlike the enlightenment brought about by the discovery of apoptotic cell death.

With this framework in mind Dr Schwartz has focused on glaucoma. As ophthalmologists know only too well, glaucoma is a “mechanical” disease caused by a blockage that interrupts the balance between aqueous humour production and outflow. The blockage causes an increase in the intraocular pressure (IOP) which subsequently leads to optic neuropathy and the death of retinal ganglion cells. Consequently, a major objective of potential therapies is to reduce IOP.

While accepting the “mechanical” component of glaucoma, Dr Schwartz’s research suggests that the disorder may also involve an inappropriate regulation of a normal autoimmune system which has strayed from the path of homeostatic balance. This paradigm shift in understanding brings into focus a new range of targets against which new drugs may be designed to affect the course of glaucoma.

**As retinal ganglion cells die, they cause changes in their immediate environment creating a hostile environment for remaining healthy neurons. These changes can be thought of as “enemies within” - as distinct from foreign invaders, such as microbes or viruses. Such internal enemies include molecules and such factors as an increase in free radicals, deprivation of growth factors, COX-2 and nitric oxide.**

If the levels of these enemies from within fall outside physiological norms, problems arise.

The immuneology text books tell us that immune B-cells and T-cells represent a bewildering repertoire of cells designed to interact with an almost infinite number of substances to defend the body. If such immune cells react to self antigens, such cells are culled in the maturation process. Faults in the system that permit T-cells to react to self antigens can lead to autoimmune disorders such as multiple sclerosis, lupus or rheumatoid arthritis.

Microglial cells are the standby immune cells of the central nervous system that maintain homeostasis. Unless well controlled, they can act in a manner to produce a range of potent immune chemicals that can end up doing more harm than good in sensitive tissues such as the eye and brain. A sub-population of immune T-cells is capable of regulating how microglia behave. Against such a background, a key therapeutic application of Dr Schwartz’s research is to harness the activity of these T-cells to stimulate microglia to protect neuronal cells.

Microglial cells in the eye and brain can clear these organs of unwanted materials; the activity of the microglia is controlled by T-cell lymphocytes. Microglia acting as protective immune cells in the brain and eye can operate at two speeds - the first speed reacts to the threat of infection from micro-organisms; however, they may also be activated in a different way. Running at a “lower” speed, the microglia can be harnessed to provide a protective role in a neurodegenerative environment as demonstrated by data produced in the lab of Dr Schwartz.

“Microglia are like the macrophages in the rest of the body,” Dr Schwartz told EuroTimes. “They recognise enemies. If you don’t control them, they react in the most robust way they know and the robust way is if there is a micro-organism producing TNFα, COX-2 and NO. However, the eye and brain are very sensitive to such strong chemicals and so what the T-cells recognising self-component in the brain or the eye (recognitions of self serves for...
New autoimmunity research owes debt to apoptosis findings

To appreciate how autoimmunity fits into the current landscape of medical research requires a little background to view such new developments in perspective. A useful starting point is the process by which cells die according to a well controlled programme. That process is known as “apoptosis.”

In the 1990s, researchers in different fields of medical research began to recognise that cells involved in apparently “failed” experiments often showed curiously regular stages of dying. That recognition set the stage for a new and exciting field of molecular biology based on the cell’s ability to control its own death.

Protective autoimmunity - a new concept

Just as apoptosis provided a new platform from which to view some old problems, recent research in immunology – including that by Dr Schwartz - may provide a new platform from which neuro-degenerative disease can be re-examined.

The field rapidly exploded and continues today unabated. That field of research was termed “apoptosis” and for those at the cutting edge of such research the discoveries were nothing less than magical. In apoptosis, researchers could view some of the very fundamental aspects of biology, thus revealing another universe previously obscured by sight.

Apoptosis reached into practically everything. Biological research was re-invigorated overnight through its capacity to permit age-old problems to be addressed under a different light. No matter where you turned apoptosis was there: leaves fell from trees due to apoptotic cell death; tiny worms sculpted their adult form by committing a very precise apoptotic cell death on a very precise number of cells; and, using the same apoptosis process, an infant’s hand in the womb transformed from a flipper-like organ into a recognisable five-digit hand. All these seemingly unrelated phenomena could be traced back to apoptosis – a form of well controlled cellular death. Re-formulating a grant application as an apoptotic research programme greatly increased your chances of securing funds. And then, there was cancer.

Cancer, rather than being a proliferative disease of uncontrollable cell growth, in the light of apoptosis, could be equally interpreted as a disease in which cells failed to die at the appropriate time. This was not merely an interesting intellectual shift in the frame of reference but rather a fundamental paradigm shift in how biologists looked at the role of death in the life of cells. Understanding the mechanics of apoptosis would open an entirely new range of cancer drug targets – finding new ways to persuade cells to die became all the rage. Today, several commercial ventures developing drugs against targets identified in the gold rush of early apoptotic research.

Conversely, neuro-degenerative disorders such as Parkinson’s, Alzheimer’s and retinal degenerations can be characterised by the opposite problem – cells keep dying when you would rather they stayed alive. It seemed that in the case of glaucoma, researchers literally stumbled across a fundamental aspect of how nature operated. Inappropriate activation, in general, caused a degenerative disease, such as Parkinson’s, while an inability to activate the caspases could lead to cancer. It turned out that a little death could be a good thing.

Of course, hindsight is always 20/20. Although much detail has been filled out since the 1990s, it is important to remember that up until that time, it was counter-intuitive to believe that living cells – with their indomitable “life-force” - could contain genetically encoded machinery primed to bring about self destruction. How could evolution permit the existence of genes that caused cell death? Within the code of life (DNA) there were written a script for death, and it took careful and patient research until it began to make sense. The phenomenon only became comprehensible when researchers began to look at the organism as a whole rather than at each isolated single cell.

Researchers now generally accept that apoptosis is a necessary safety valve to kill off infected or genetically “AWOL” cells to spare the organism from the spread of disease. This is the cells “candyide” option when all other avenues of escape have been exhausted. Clearly, Mother Nature is smarter than we thought.

To be initially an agonist of self antigen – that is tolerated by the central nervous system and is beneficial rather than destructive.

Multiple sclerosis treatment points to new possibilities

One way to go with this is to do what you are doing with vaccination against influenza. You don’t take the living virus. You attenuate it or kill it. Along the exact same analogy, we wanted to immunise with a self antigen which is not very aggressive. Copaxone is a weak agonist of self antigen, so when you immunise you get T-cells. These T cells are not very strong; they are not proliferative, so you get a modest immune response. The research has now progressed well beyond the confines of Dr Schwartz’s lab at the Weizmann Institute. Significant commercial interests have also recognised the potential to harness protective autoimmunity in the treatment not only of glaucoma but possibly in a number of other neuro-degenerative disorders. Teva Pharmaceuticals Ltd and Proneuron Biotechs, both with corporate offices in Israel, are prudently in a licence agreement to begin Phase II clinical trials with an altered formulation of Copaxone for the treatment of glaucoma.

Although such research has shown that vaccination with Copaxone® may help fight glaucoma - particularly in combination with anti-hypertensives - Dr Schwartz cautions that vaccination does not promise a cure.

“Therapeutic vaccination will not prevent the onset of glaucoma but it may provide a way to prevent or at least slow down its propagation,” she says. “Vaccination with self- or self-like antigens may be viewed as boosting the physiological mechanism of neuroprotection. Accordingly, patients with glaucoma are likely to benefit from a safely boosted immune response, which is mediated by weak self-reacting T cells, and can be viewed as helping the body to protect itself against destructive self compounds emerging as a result of an increase in IOP and causing tissue loss.”

Michal Schwartz PhD
michalschwartz@weizmann.ac.il