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Editorial

Astrocytes and glaucomatous neurodegeneration

1. The Lasker/IRRF Initiative for Innovation in Vision Science

Glaucoma is the leading cause of irreversible blindness throughout the world (Kingman, 2004; Resnikoff et al., 2004). 60.5 million people were affected worldwide in 2010 (Quigley and Broman, 2006), a number that is projected to increase to 111.8 million in 2040 (Tham et al., 2014). Glaucoma is an optic neuropathy with typical defects in optic disc structure and visual function leading to a characteristic pattern of visual field loss (Foster et al., 2002; Quigley, 2011). Multiple prospective randomized multi-center studies have identified intraocular pressure (IOP) as a critical risk factor for the pathogenesis of glaucoma (Collaborative Normal-Tension Glaucoma Study Group, 1998a, b; Kass et al., 2002; Leske et al., 2003; The AGIS Investigators, 2000). Consequently, glaucoma treatment aims at medically or surgically reducing IOP, which is currently the only proven method to treat glaucoma (Boland et al., 2013). Still, while therapy reduces the rate of progressive vision loss over the lifetime of many patients, the loss of visual field continues in a certain percentage (Quigley, 2011). Moreover, the available surgical techniques that are required in advanced forms of glaucoma to lower IOP may lead to vision-threatening complications. Overall, the current situation makes it mandatory to further study the mechanisms that are behind optic nerve axonal degeneration in region of the ONH with the ultimate goal to identify novel ways to treat glaucoma.

There is considerable evidence pointing to the optic nerve head (ONH) as the critical site in the initiation of glaucomatous damage. Support for this assumption comes from experimental studies in monkey (Quigley et al., 1981) and mouse (Howell et al., 2007) models of glaucoma. In addition, there are clinical entities that involve the ONH and mimic the phenotype of glaucoma, such as anterior ischemic optic neuropathy (AION), drusen at the optic nerve head, chronic papilledema, juxtapapillary choroiditis and optic nerve head splinter hemorrhages (Tamm et al., 2013). Despite considerable research efforts over the past decades, our knowledge of the cellular and molecular mechanisms that cause glaucomatous optic nerve axonal degeneration at the ONH remains largely incomplete.

The Lasker/IRRF Initiative for Innovation in Vision Science is a ten-year collaboration, launched in July 2008, between the Albert and Mary Lasker Foundation (Lasker)[1] and the International Retinal Research Foundation (IRRF).[2] The Initiative was designed to identify knowledge gaps in retinal and ophthalmic research and propose innovative strategies to accelerate the discovery of sight-saving treatments and prevention of retinal degenerative diseases using novel scientific, engineering and technological approaches. The Initiative's first report, Astrocytes and Glaucomatous Neurodegeneration, was published in November 2010 (a copy of the report is available at http://www.irrfonline.org/laskerirrf.html or http://www.laskerfoundation.org/programs/irrf.htm). Since then, there is general agreement that significant scientific progress has occurred in the field. For example, it now is commonly accepted that astrocytes are a critical element of glaucoma pathophysiology, and advances in understanding the optic nerve head using new animal models have moved the field considerably. In 2014, the Initiative's Joint Advisory Board agreed that it would be valuable, both to the Initiative and to vision research, to evaluate where the field is now, whether and how the 2010 report stimulated innovative lines of research, what scientific hurdles have been overcome and what problems now confront the field. A Steering Committee was established to define goals and key issues for exploration by invited participants, which included many scientists from the first Initiative as well as some additional scientists.

In March 2015, following an invitation by the Lasker/IRRF Initiative for Innovation in Vision Science, more than 40 scientists from all over the world met at the Howard Hughes Medical Institute Janelia Research Campus in Ashburn, Virginia (Fig. 1). They discussed the current status in the field and identified questions, topics and experiments that should be addressed within the next five years.

The meeting format strongly emphasized discussion and

[1] About the Albert and Mary Lasker Foundation: Founded in 1942, the Albert and Mary Lasker Foundation envisions a healthier world through sustained support for basic and clinical medical research. The Foundation works to accomplish its mission through education and advocacy and, most notably, through a prestigious annual awards program. Lasker Award winners are selected by their peers, who, like themselves, include the world's most accomplished and well-respected medical research scientists, and thus the award represents a special honor. The Foundation's education and advocacy missions focus on engaging the public and policymakers on the importance of robust medical research programs and the funding to make them possible. The Lasker Foundation is also dedicated to supporting and inspiring the next generation of research scientists. For more information about the Lasker Foundation and its programs, visit http://www.laskerfoundation.org.

[2] About the International Retinal Research Foundation: The International Retinal Research Foundation (IRRF) upholds a commitment to accelerate and sustain targeted research efforts into the diseases of the human eye, especially those affecting the retina and macula, to discover the causes, preventions, and cures of retinal and macular degenerative diseases and diabetic retinopathy. The IRRF accomplishes its mission by providing financial support for vision research directly, as well as through training fellowships, public awareness programs, and the promotion of the exchange of research findings. For more information about the IRRF, please visit www.irrfonline.org.

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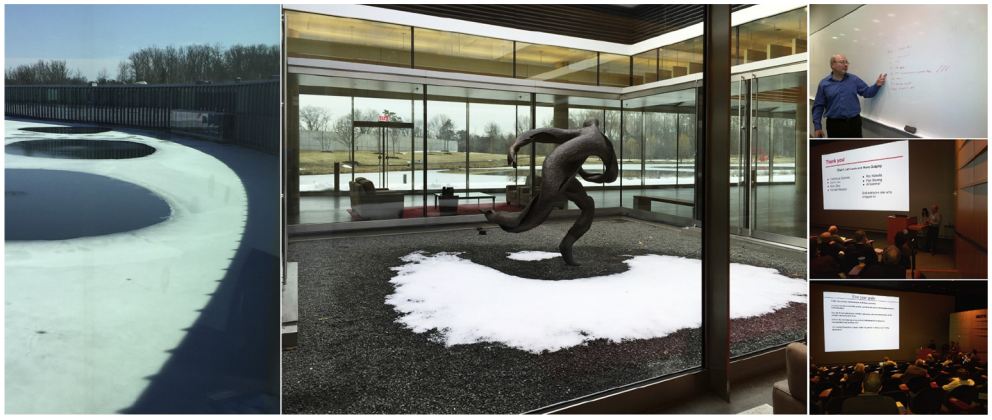

Fig. 1. Impressions from the March 2015 Lasker/IRRF Initiative for Innovation in Vision Science meeting "Astrocytes and Glaucomatous Neurodegeneration" at the Howard Hughes Medical Institute Janelia Research Campus, Ashburn, Virginia.

concentrated on questions within five general areas of research:

1. Glial Cells, Ganglion Cells, and the Optic Nerve Head
2. Astrocytes and Biomechanics
3. Inflammation and Glaucomatous Neurodegeneration
4. Optic Nerve Regeneration and Neurorepair
5. Neuroprotection and What Is Needed Clinically

All areas were covered in presentations and keynote lectures followed by specific targeted sessions for which the steering committee had identified specific points for discussion. The ideas that came up at the targeted session were presented to all participants at the meeting and discussed. Finally, co-chairs and scribes summarized the results of each targeted session in five review articles that are now published in this special issue of Experimental Eye Research. The first article by Tamm and Ethier (2017, in press) reviews the possible molecular and cellular mechanisms that are behind axonal damage in glaucoma. An increase in strain of the peripapillary sclera that surrounds the ONH is identified as a possible initiating event that may trigger astrocyte reactivity in the ONH, putatively via transforming growth factor-β signaling. Reactive astrocytes in the ONH are expected to change homeostasis in the ONH microenvironment causing axonal degeneration. In a second article, by Stowell et al. (2017, in press), the current concepts on the biomechanical changes in the ONH and the exciting data that have been generated on this issue in the last few years are discussed. It is expected that more knowledge on the biomechanical forces that act on this tissue in the normal eye and in those with glaucoma is critical to understand the mechanisms that lead to structural changes at the ONH.

An entirely novel concept to explain axonal damage in glaucoma is presented in a third article by Williams et al. (2017, in press). Here the available data that point to a neuroinflammatory origin of optic nerve damage in glaucoma are discussed and strategies are introduced that will help to explore this concept in more detail. Calkins et al. (2017, in press) provide a fourth article that highlights the available options to develop regenerative therapies for optic nerve axons that were damaged in glaucoma. They discuss the problems that need to be solved, such as preventing astrocyte reactivity and neuroinflammation at the ONH through which regenerating axons need to pass, but also the challenge to ensure that the connections with appropriate targets are formed in the brain. Finally, in a fifth article by Levin et al. (2017, in press), the requirements are discussed that are needed to initiate a neuroprotective therapy that will work not only in animal models with glaucoma, but one that also has the potential to be translated into clinical practice.

2. Concluding Remarks

As noted in the Concluding Remarks at the end of the Initiative's first report, glaucoma remains an intractable condition. But progress is being made, as detailed in this report; new ideas and approaches are being pursued and new facts and concepts elucidated. The energy, enthusiasm and imagination shown by the participants at the Janelia Research Campus meeting in March, 2015 bodes well for the future and for a breakthrough in dealing with this blinding disease. It is useful to note that glaucoma remains second on the list of blinding eye diseases in the United States, surpassed only by severe cataracts. Whereas some light perception remains in those suffering from severe cataracts, total blindness occurs in those with late-stage glaucoma. The need for a way to prevent glaucoma is very great, and the Lasker/IRRF Initiative hopes that the two meetings it has sponsored on glaucoma have helped get us closer to the day when this dreaded disease can be prevented.

Steering committee

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