Inhibition as Potential Therapeutic Target in Inflammation, Insulin Resistance, and Heart Failure

Written by Muriel Cunningham

Ippei Shimizu MD, PhD, Boston University School of Medicine, Boston, Massachusetts, USA, summarized a body of work investigating the pathways and relationships between obesity, inflammation, insulin resistance, and heart failure.

p53 is an important tumor suppressor protein involved in DNA repair, apoptosis, and cell cycle regulation. Earlier work demonstrated that p53 in adipose tissue regulates systemic insulin resistance in obesity [Minamino T et al. *Nat Med* 2009]. Additionally, in mice that underwent thoracic aortic constriction (TAC; a model for heart failure), an increase in p53 expression, systemic insulin resistance, and adipose tissue inflammation was observed. When TAC was performed on p53 knockout mice, reduced adipose tissue inflammation and insulin resistance were observed. This and additional experiments led to the conclusion that heart failure upregulates p53 in adipose tissue, which in turn leads to inflammation of adipose tissue and systemic insulin resistance [Shimizu I et al. *Cell Metab* 2012].

When the heart is overloaded, cardiac hypertrophy results, ultimately leading to heart failure if the overload is sustained. Cardiac angiogenesis can prevent the progression to heart failure and, conversely, cardiac function worsens when cardiac angiogenesis is inhibited. Dr. Shimizu believes that basal cardiac insulin signaling is critical in maintaining cardiac homeostasis; however, when TAC was performed in mice with deleted cardiac insulin receptors, cardiac function was improved and less hypertrophy was observed. This result suggested that excessive cardiac insulin signaling may induce cardiac hypertrophy and deteriorate cardiac function during pressure-overload [Shimizu I et al. *J Clin Invest* 2010]. In summarizing their overall findings from multiple experiments, Dr. Shimizu said that heart failure upregulates sympathetic activity and lipolysis, leading to increased adipose tissue p53 levels. This in turn results in systemic insulin resistance that exacerbates heart failure.

In terms of potential therapies, it is unlikely that p53 itself is a viable therapeutic target. "p53 is the 'guardian of the genome' and inhibition of this molecule is problematic because it promotes cancer. It is critically important to find a molecule located downstream of p53," said Dr. Shimizu. Semaphorin 3E and its receptor Plexin-D1 (Sema3E/PlexinD1) may be a potential therapeutic pathway. Semaphorin-plexin signaling regulates immune cell function and both are involved in vessel formation, but their association with obesity is currently unknown.

Dr. Shimizu shared some recent data regarding his Sema3E/PlexinD1 research. A murine obese model was created by giving mice a high-fat, high-sucrose diet. This led to diet-induced obesity with associated adipose inflammation and impaired glucose metabolism. Significant increases in both the circulating level of Sema3E and expression in adipose tissue were observed in these mice. The PlexinD1 level also was also increased in the obese adipose tissue, primarily in macrophages. Results from a migration assay indicated that Sema3E functions as a chemo-attractant for macrophages, and that this chemo-attractant activity is plexinD1 dependent. In his concluding remarks, Dr. Shimizu said he believes that their data suggest that the inhibition of the Sema3E/PlexinD1 pathway is a potential treatment target in adipose inflammation and metabolic dysfunction in obesity.

Novel Pharmacotherapies in the Treatment of Diabetic Retinopathy

Written by Brian Hoyle

Arup Das, MD, PhD, University of New Mexico School of Medicine, Albuquerque, New Mexico, USA, provided an overview of emerging pharmacotherapies for the treatment of diabetic retinopathy (DR). In the late 1980s it was determined that microaneurysms, the earliest clinical lesions of DR, occur due to loss of pericytes that, in turn, spur endothelial cell proliferation in the eye [Kelly C et al. *J Cell Biol* 1987; Orlidge A, D'Amore PA. *J Cell Biol* 1987; Das A et al. *Exp Eye Res* 1988]. Nonproliferative DR includes diabetic macular edema (DME), with the hallmark of hard exudates, edema, and hemorrhage.

The cell proliferation (angiogenesis) that occurs in proliferative diabetic retinopathy (PDR) has been hypothesized to result from the hypoxia that can occur during advanced stages of the disease. The resulting elaboration of angiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor, and insulin-like growth factor, spurs vessel formation in the eye. These new vessels result in vitreous hemorrhage and sometimes traction retinal detachment, causing severe visual loss.

LASER TREATMENT

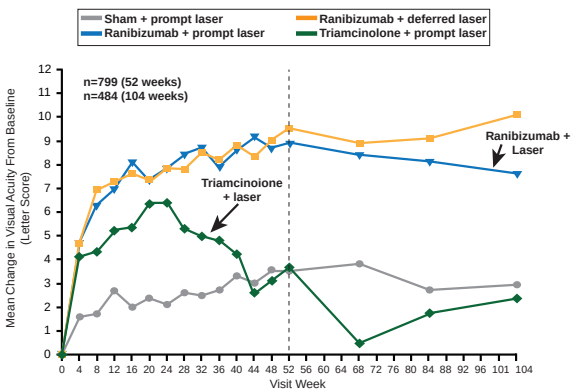
The current standard treatment for PDR is panretinal laser photocoagulation (PRP). Untreated eyes incur more severe visual loss than laser-treated eyes as shown by the DR study.

While PRP laser treatment has undisputed benefits in eyes with PDR, potential complications include loss of peripheral vision and loss of night vision [Bressler NM et al. *N Engl J Med* 2011]. A clinical trial is under way to examine whether anti-VEGF injections are more beneficial than the current PRP laser treatment.

TARGETING OF VEGF

A more recent approach has been the targeting of VEGF, which is upregulated in DME, particularly in extensive DME [Funatsu H et al. *Ophthalmology* 2003]. Trials of various VEGF- targeted approaches, including monoclonal antibodies (pegaptanib, bevacizumab, ranibizumab, VEGF trap), have yielded encouraging results (Figure 1; Table 1) [Elman M et al. *Ophthalmology* 2010]. However, ranibizumab is the only Food and Drug Administration-approved drug now for treatment of DME.

Figure 1. Ranibizumab in Diabetic Macular Edema: DRCR Protocol I



Reproduced from Elman M et al. Randomized Trial Evaluating Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema. *Opthalmology* 2010;117(6)1604-1077. With permission from Elsevier.

Table 1. Diabetic Retinopathy Trials With Anti-VEGF Agents

Study	Drug	Comparator	Duration	Potential Benefit Reported
RESOLVE	Ranibizumab	Sham	1 year	+11.8 vs -1.4
RIDE/RISE	Ranibizumab	Sham	3 years	+15.6/+12.8 vs +7.6
RESTORE	Ranibizumab	Laser	1 year	+6.1 vs +0.8
READ-2	Ranibizumab	Laser	2 years	+7.7 vs +5.1
DRCR Protocol I	Ranibizumab	Laser	3 years	+7.7 vs +5.1
DA VINCI	Aflibercept	Laser	1 year	+9.7/+13.1 vs -1.3
BOLT	Bevacizumab	Laser	2 years	+8.6 vs -0.5
A5751013	Pegaptanib	Standard care	2 years	Yes

Particularly for center-involved DME, the consensus is that anti-VEGF strategies slow disease progression, reverse features of DR, and delay the need for laser treatment. However, residual macular edema is problematic. Several intravitreal anti-VEGF injections are necessary to treat DME, and the effect of these drugs are not as robust as they are in PDR. Furthermore, targeted, chronic obliteration of VEGF may be toxic, triggering the death of cone receptors required for central and color vision [Kurihara T et al. *J Clin Invest* 2012].

STEROID THERAPY

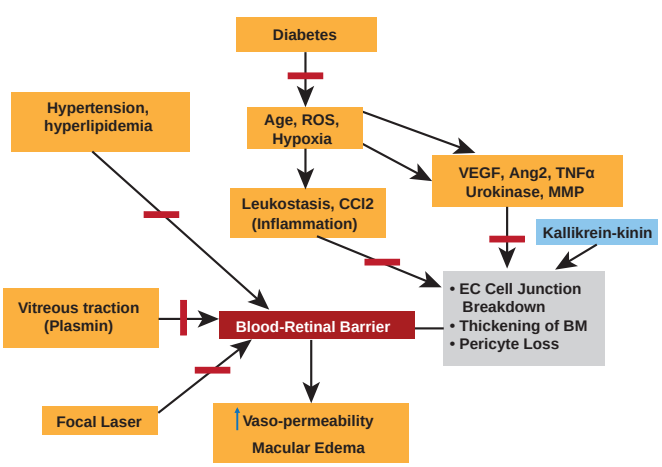
The use of steroids to relieve inflammation that can exacerbate DME is an attractive approach. The two recent randomized, double-masked, parallel-group, multicenter Fluocinolone Acetonide for Macular Edema studies [FAME; NCT00502541, NCT00576459] have been particularly noteworthy. Nonbiodegradable cylindrical implants harboring fluocinolone acetonide were inserted into patient eyes. The primary outcome (improved vision of >15 letters) was achieved by 29% of the collective patients at 3 years versus 19% for the sham group. Patients with a longer history of DME showed a greater benefit. Yet, 89% of treated patients required cataract surgery and up to ~2% required trabeculoplasty (Food and Drug Administration approval awaiting additional data).

OTHER APPROACHES

Angiopoietin 2 is another potential target for DME. This proinflammatory cytokine has been linked with increased vascular permeability in DME. Nonsteroidal anti-inflammatory drugs may have therapeutic value. High daily doses of aspirin may slow the development of retinal microaneurysms, although this conclusion is equivocal. Tumor necrosis factor-α is another pro-inflammatory cytokine that had reported value in DME in a small Phase 3 trial [Sfikakis PP et al. *Diabetes Care* 2010]. Other potential targets include chemokines like CCL2, and kallikrein-kinin system.

DME involves a complex interplay of a variety of risk factors and molecular pathways (Figure 2). Research over the past 3 decades has considerably clarified the picture. But, more remains to be done, particularly concerning the therapeutic tools and their optimal concentrations.

Figure 2. Summary of Factors Important in DME



BM=basement membrane; EC=endothelial cell; MMP=matrix metalloproteinases; ROS=reactive oxgen species; TNF-α=tumor necrosis factor-α; VEGF=vascular endothelial growth factor.