**Valvular Heart Disease: Understanding the Genetic Components**

**Daniel Rayner**

Over the last couple of decades, only two classes of drugs have been approved for use in patients with influenza: M2 ion-channel inhibitors (e.g., rimantadine) and neuraminidase inhibitors (e.g., oseltamivir). However, resistance to these drugs has been increasing, with circulating influenza strains now predominantly resistant to M2 ion-channel inhibitors. Even resistance towards the current frontline for influenza treatment, neuraminidase inhibitors, is a health concern, as demonstrated by the oseltamivir-resistant influenza A(H1N1) pandemic during the 2008-2009 season.

Approved by the U.S. Food and Drug Administration (FDA) in October 2018, baloxavir marboxil (BM) is a novel anti-influenza drug that targets the RNA-dependent RNA polymerase (RdRp), the heterotrimeric enzyme responsible for transcription of viral mRNA. Specifically, BM inhibits the polymerase acidic (PA) protein, the subunit responsible for cleaving the 5’ end of host pre-mRNA, which is subsequently used as a primer for viral mRNA production. However, BM is not exempt from resistance mutations —I38T/F3 point mutations in the PA subunit were observed in 2.2% and 9.7% of BM recipients in phase II and phase III clinical trials, respectively. These substitutions were found to reduce the viral strains’ susceptibility to BM by more than a factor of ten in those infected with influenza A(H1N1).

The presence of a new anti-influenza drug on the market may allow for the use of combination therapies for patients with complicated influenza infections. The combination of BM and oseltamivir was more effective than each monotherapy in influenza infections. The presence of a new anti-influenza drug on the market may allow for the use of combination therapies for patients with complicated influenza infections. The combination of BM and oseltamivir was more effective than each monotherapy in influenza infections.

Recently, research by Wünemann and colleagues has led to the discovery of another monogenic VHD gene, *ADAMTS19*, which encodes an enzyme responsible for extracellular matrix modelling activity. Using whole-exome sequencing on two consanguineous families with prevalent early-onset VHD, researchers found that affected individuals had homozygous, loss-of-function alleles in *ADAMTS19*. Supplemented with an *Adams19* knockout murine model, Wünemann and colleagues hypothesize that loss of *Adams19* interferes with shear stress signalling in the endothelial cells of the aortic valve, inducing upregulation of the transcription factor Klf2. Klf2 regulates Wnt9b, the ligand responsible for the remodeling of cardiac cushions into mature heart valves. This dysregulation of Klf2 leads to VHD through extracellular matrix disorganization, as well as increased cellularity and proteoglycan deposition in the valves.

Improving our understanding of the genetic components, molecular pathways, and cellular mediators involved in the development of the disease may aid in treating VHD. Not only can it improve genetic screening for high-risk individuals, but it also opens up an avenue for potential VHD pharmacological therapies, which can delay or halt disease progression.

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**THE FARNESOID X RECEPTOR: A NOVEL TARGET FOR HEPATOCELLULAR CARCINOMA**

SHADI SADEGHIAN

The Farnesoid X Receptor (FXR) is a nuclear receptor expressed in the liver that is known to maintain bile acid homeostasis. But changes in FXR expression and activity can lead to pathological changes, such as uncontrolled cell growth in the liver.

Under FXR-deficient conditions (commonly observed in HCC) the FXR-3 pathway is activated by an increase in the expression of an inflammatory cytokine, IL-1β, which subsequently increases levels of IL-6. The reason for this upregulation is the increase in bile acid concentration resulting from FXR deficiency. This bile acid build-up induces cholestasis and hepatic inflammation, thus recruiting various inflammatory cytokines. As IL-6 binds to its receptor, the IL-6/Jak-2/STAT-3 pathway is activated. As a result, newly formed STAT-3 homodimers are able to activate downstream genes responsible for hepatic carcinogenesis.

Various studies have demonstrated that FXR ligands cause an upregulation of FXR expression and reduce the cholestasis that initiates this carcinogenic cycle. Cell cycle analyses have shown that FXR ligation increases the number of HepG2 (HCC) cells at the cell cycle arrest phase, and decreases the cells in the synthesis phase. All of this demonstrates the ability of FXR to mitigate uncontrolled cell growth in the liver.

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**RHO KINASE INHIBITORS: MANIPULATING CELL SHAPE FOR TREATMENT OF GLAUCOMA**

SHADI SADEGHIAN

Glaucoma is the second leading cause of irreversible blindness worldwide. This condition involves the degeneration of retinal ganglion cells and is characterized by elevated intraocular pressure (IOP). The problems arising in glaucoma originate in the anterior chamber of the eye, where aqueous humour (AH) drainage via the trabecular meshwork (TM) is impeded. Since the damage to retinal ganglion cells in glaucoma is irreversible, the goal of treatment is to preserve remaining visual acuity by mitigating high IOP.

It was first noticed in the 1990s that the pharmacological manipulation of the cytoskeleton of TM cells decreases aqueous humor outflow resistance, thus significantly reducing IOP. Rho kinase inhibitors play a key role in the rigidity of the cytoskeleton of TM cells and thus have been of particular pharmacologic importance, as they influence AH drainage efficiency. The GTase Rho, when bound to guanosine triphosphate (GTP), is able to activate Rho kinase. Rho kinase is then able to undergo a series of biological reactions that change the properties of the cytoskeleton, which dictates the cell’s morphology. By this mechanism, the protein increases the rigidity of the TM cells, affecting their mobility.

It was observed that administration of 0.25% of a Rho-kinase inhibitor twice per day reduced IOP by 28%, or around 6.8 mmHg. Several other studies have had similar findings, demonstrating the promise of this practice.

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