H8 The Role of P2Y2 Receptors in the Pathogenesis of Hantavirus Cardiopulmonary Syndrome (HCPS)

Casey P. Bitting, DO, University of New Mexico School of Medicine, Univ of NM Health Science Ctr, Msc08 4640, Dept of Pathology, 1 University of NM, Albuquerque, NM 87104; Virginie Bondu, University of New Mexico School of Medicine, 915 Camino De Salud NE, BRF 336, Albuquerque, NM 87131; Valerie Poland, BA, Office of the Medical Investigator, 1101 Camino de Salud, NE, Albuquerque, NM 87102; Sarah Lathrop, DVM, PhD, 4920 Edwards Drive, NE, Albuquerque, NM 87111; Daniel Lawrence, PhD, University of Michigan, 2800 Plymouth Road, Ann Arbor, MI 48109; and Tione Buranda, PhD, University of New Mexico School of Medicine, 1 University of New Mexico, Albuquerque, NM 87131*

After attending this presentation, attendees will: (1) better understand the role of receptor expression and activation in productive hantavirus infection; (2) recognize the association of hyperinflammation and procoagulatory state with HCPS pathogenesis; and, (3) recognize the potential for translation of the HCPS disease mechanism to clinical intervention.

This presentation will impact the forensic science community by providing recent insight into the pathogenesis of HCPS, a poorly understood and rapidly fatal illness. This insight is possible due to the unique affiliation of the University of New Mexico School of Medicine with the New Mexico Office of the Medical Investigator and highlights the importance of collaborative efforts between forensic pathologists and research entities.

HCPS is characterized by the loss of pulmonary vascular endothelial integrity, resulting in massive, acute pulmonary edema.[1-3] There is no curative therapy, and treatment of severe disease is supportive, including the use of Extracorporeal Membrane Oxygenation (ECMO).[4] Hantaviruses are known to primarily infect capillary endothelial cells, most prominently in the lungs, spleen and kidneys; however, the mechanisms of infection and pathogenesis have remained poorly understood.[5,6] Although pathogenic hantaviruses have been shown to bind the inactive, bent $\alpha v\beta_3$ integrin structure on endothelial cells, the identity of additional proteins involved in integrin activation and hantavirus infectivity have been heretofore unknown.[7] Recent studies revealed that integrin activation is mediated by the $P2Y_2$ receptor ($P2Y_2R$), a purinergic receptor that responds to Adenosine Triphosphate (ATP) and Uridine Diphophate (UDP). P2Y receptors are ubiquitous G Protein-Coupled Receptors (GPCRs) known to participate in a variety of biological functions including immune response and platelet aggregation.[8] Considering that ATP and other nucleotides act as Damage-Associated Molecular-Pattern (DAMP) molecules released at high local levels following infection and tissue damage, it is not surprising that $P2Y_2R$ is upregulated in the setting of inflammation, including infection.[9-11] In addition to being associated with hyperinflammation and tissue damage during sepsis, $P2Y_2R$ has also been associated with procoagulatory states, including Tissue Factor (TF) and Plasminogen Activator Inhibitor-1 (PAI-1) upregulation.[10,12-16] Recently, a proteomic study of HCPS patient plasma found that activated PAI-1 levels increase up to 100-fold within the 48 hours prior to death, indicating a procoagulatory state.[17] Given the mutual association of $P2Y_2R$ expression and HCPS with a procoagulatory state, it was hypothesized that $P2Y_2R$ contributes to the pathogenesis and severity of HCPS. To test this hypothesis, a gene expression assay was used to analyze $P2Y_2R$ expression in formalin-fixed, paraffin-embedded tissue of HCPS subjects whose deaths were investigated by the New Mexico Office of the Medical Investigator (OMI). The mean $P2Y_2R$ mRNA expression in HCPS lung tissue was 22.2 ± 4.5-fold higher than in controls (gunshot fatalities). In addition, $P2Y_2R$ mRNA expression correlated positively with plasma levels of PAI-1 measured in HCPS decedents. Lastly, the preliminary

data show that HCPS plasma stimulates endothelial cells to upregulated $P2Y_2R$ mRNA during short-term culture, and that this upregulation correlates with disease severity. Altogether, it is concluded that $P2Y_2R$ expression is upregulated in HCPS and that a proteomic milieu of circulating factors contributes to this upregulation. Thus, these indices of a procoagulatory state might be useful as prognostic biomarkers for HCPS severity and prognosis. Furthermore, studies indicate a need for further study of $P2Y_2R$ for consideration as a therapeutic target in the treatment of HCPS.

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