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EPIGENETIC RE-PROGRAMMING OF PLASMA MICROVESICLES IN SEPSIS

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Background: Sepsis microvascular dysfunction embraces different cellular components including endothelial cells, in which it increases its permeability and activation to shed extra microparticles (MPs) to transport a unique cellular signaling to the recipient cells. In this study, we observed that microparticles can retain different epigenetic components as miRNA, mRNA of DNMTs and HDACs from parent cells that can transfer to naïve target cells. Importantly, in sepsis, MPs production is increased. Increased expression of DNMTs results in promoter hypermethylation which can suppress transcription of not only a single gene but networks of genes with systemic effects. Sepsis is an inflammatory insult which can result in vascular dysfunction leading to systemic shock and eventual death.

Aim: The aim of this study is to distinguish the role of sepsis microparticles in systemic immunosuppression process and the impact of these particles upon cellular targets and survival mechanisms to allow better diagnostic tools and potential novel therapeutic approach during infection and trauma.

Methodology: Endothelial cells (HUVEC) and naïve monocytes treated with MPs from patients with sepsis demonstrated dramatically reduced of anti-inflammatory genes, TGF-β, TNF-α expression and some of autophagy molecules (ATG5, ATG7 and LC3) due to hypermethylation of their promoter. These data demonstrate that mRNAs of epigenetic regulators including DNMTs are highly expressed in plasma MVs in patients with sepsis and can be transferred to naïve cells through MVs and cause pro-inflammatory cytokine gene silencing and autophagy repression in monocytes. Further, MVs per mL plasma on day 1 alone significantly correlated with death by day 5 (r=0.7125 and p=0.0042). Using immunostaining techniques and flow cytometer, we found the major source of plasma MVs in the critically-ill, non-septic control patients shifted from monocytes (Mo) to endothelial cells (EC) in the SS patients (Control: Mo 63.6% and EC 7.4% and SS: Mo 12% and EC 58.7% qualitatively). Focusing our study on SS patients who lived and SS patients who died by day 5, our data shows that while total DNMT mRNA copy numbers per plasma MV are significantly higher over days 1 and day 3 in those SS patients who lived, the ratios of DNMT1 (maintenance DNA methylation) and the combination DNMT3A and DNMT3B (de novo DNA methylation) are reversed on days 1 and 3 (SS Lived: DNMT3A/3B-to-DNMT1: day 1=0.68 and day 3=0.87; SS Died: DNMT3A/3B-to-DNMT1: day 1=2.49 and day 3=2.94). Finally, MV DNMT3A/3B mRNA from day 1 samples positively correlates with reduced survival (r=6261 and p=0.0165). Targeting of circulating MVs with commercially available inhibitors of DNMTs may be a therapeutic strategy in specific patients with deregulated epigenetic mechanisms to limit both early and chronic consequences.

Results: We found that MPs from patients with septic shock and septic had significantly increased mRNA for DNMTs compared to MPs from patients with critical illness without sepsis and from normal healthy adults over the course of 5 days. Remarkably, we noticed that DNMT1 and -3a mRNA has the highest gene expression in sepsis MPs compared to other DNMTs. Additionally, naïve monocytes treated with MPs from patients with sepsis demonstrated increased expression of DNMTs. At the same time decreased expression at 24 hours.

Biography

My research focuses on the genetic mechanisms and regulatory pathways involved in pulmonary disease. In my graduate study I had focused on the role of microRNAs and epigenetic regulators in disease pathology. Specifically, we had identified alterations in gene regulation that correlates with clinical severity of disease in IPF. This has allowed us to target potential therapies, some of which have shown significant promise in our small animal models. While my current focus is on patients with IPF, these pathways allow diverse application too many fields of study. We have developed several collaborations with clinicians and researchers a like examining epigenetic regulation in diseases such as breast cancer, sepsis and acute respiratory distress syndrome. The central theme of my research is to identify epigenetic mechanisms by which prolonged macrophage survival can amplify the immune response and contribute to cancer, metastasis, Autophagy, chronic lung inflammation in idiopathic pulmonary fibrosis (IPF) and other inflammatory lung diseases.

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