**Supplemental Figure Legends**

**Supplemental Figure 1: Functional Enrichment Analysis**. Functional annotation clustering of DMR-associated genes showing top 10 clusters ranked by fold gene enrichment. Analysis was performed using the DAVID functional annotation tools (https://david.ncifcrf.gov). MHC class II = major histocompatibility complex class II. B) Jensen diseases association map of DMR-associated genes.

**Supplemental Figure 2:** **Changes in gene expression for DMR-associated genes during sepsis**. Bar graphs displaying the number of external gene expression datasets (comprising septic and non-septic patients) in which the DMR and not-DMR associated genes are differentially-expressed. (A) Comparing not-DMR-associated genes showing differential gene expression (black bars) vs DMR-associated genes showing differential gene expression (gray bars) (p value = 0.009). (B) Comparing not-DMR-associated genes showing expression change ≥ 1.5 fold (black bars) vs DMR-associated genes showing expression change ≥ 1.5 fold (gray bars) (p value = 3 x 10-5). C) Beta-methylation difference vs mean log fold change in gene expression for DMR-associated genes with beta-methylation difference ≥ 0.02 and absolute log fold change in expression ≥ 0.58 (50% change in expression). Genes with the highest beta-methylation differences and expression changes are labeled. CD177, NB1 Glycoprotein; E2F7, E2F transcription factor 7; TK1, thymidine kinase 1; ATP8B4, ATPase phospholipid transporting 8B4; HLA-DRB1, human leukocyte antigen DRB1; HLA-DQB1, human leukocyte antigen DQB1; MAD1L1, mitotic arrest deficient 1 like 1; GRLF1, Rho GTPase activating protein 35; PFKFB3, 6-phosphofructo-2-kinase; RAB32, RAB32, member RAS oncogene family; KLHDC7B, kelch domain containing 7B; CPEB4, cytoplasmic polyadenylation element binding protein 4; MPO, myeloperoxidase; SLC28A10, solute carrier family 28 member 10; C3AR1, complement C3a receptor 1; DKFZp761E198, adaptor related protein complex 5 beta 1 subunit; CD3D, CD3d molecule; SLC45A4, solute carrier family 45 member 4; TESC, tescalcin.

**Suppplemental Figure 3: Clinically relevant correlated differential methylation modules.** WGCNA analysis correlating methylation modules with clinical features including survival to hospital discharge (Survival), vasopressor requirement (VasoPres), severity of illness (MODS), ICU length of stay (ICU D/C), and hospital length of stay (Hosp D/C) in (A) septic patients and (B) non-septic patients. Direction of methylation change is indicated in color (see scale). Modules showing significant correlations are highlighted. C): Preservation of WGCNA methylation modules between septic and non-septic cohorts. Two separate comparisons are shown: septic methylation modules compared with non-septic methylation modules (Septic vs Non-Septic) and non-septic methylation modules compared with septic methylation modules (Non-Septic vs Septic). Zsummary ≤ 2 implies no evidence for module preservation, 2 < Zsummary < 10 implies weak evidence of preservation and Zsummary ≥ 10 implies strong evidence for module preservation.

**Supplemental Figure 4: Cell proportions for septic and non-septic patients in the EPSIS cohort.** Estimated cell counts were drived using the Houseman deconvolution method [47] while observed cell counts were obtained from patients on Day 1 of ICU admission. In both cases cell counts are not significantly different between septic and non-septic patients. CD8, CD8+ T cells; CD4, CD4+ T cells, NK, natural killer cells; Bcell, B cells; Mono, monocytes; Gran, granulocytes; Neut, neutrophils; Lymph, lymphocytes .