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Elevated expression of C/EBPβ in myeloid progenitors during sepsis promotes chronic immunosuppression

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Backgound: The immune response to sepsis rapidly shifts from an early/acute hyperinflammatory reaction to a protracted state of immuunosuppression. Sepsis accelerates myeloid cell generation to compensate for the rapid mobilization of the myeloid progenitors from the bone marrow. This inflammation-driven myelopoiesis, however, generates myeloid progenitors with immunosuppressive properites (MDSCs), which expand markedly in the later phases of sepsis. Repressor MDSCs contribute to high mortality rates in mouse and human sepsis.

Purporse: To determine whether the myeloid related transcription factor C/EBPb plays a role in MDSC expansion.

Methods: We used a murine model with myeloid-restricted deletion of the C/EBPb, where the Cebpb allele is only inactivated in the myeloid lineage. Sepsis was induced by cecal ligation and puncture, and mice received limited antibiotic treatment, which produces an acute/early phase followed by a chronic/late immunosuppressive phase.

Findings: C/EBPb myeloid cell-deficient mice did not generate MDSCs nor develop immunosuppression and survived sepsis. Surprisingly, septic survivor mice could generate $Gr1^+CD11b^+$ myeloid progenitors similar to control sham-operated mice. Morover, C/EBPb-deficient $Gr1^+CD11b^+$ cells differentiated normally in response to growth factors and adoptive transfer of C/EBPb-deficient $Gr1^+CD11b^+$ cells from late septic mice exacerbated inflammation in control mice undergoing early sepsis, confirming they were not immunosuppressive. Mechanistically, we found that C/EBPb induction in myeloid cells promoted expression of miR-2 1 and miR-181b immune repressor mediators in sepsis MDSCs.

Conclusion: Sepsis-induced C/EBPb initiates myeloid progenitor reprogramming into MDSCs with chronic immunosuppressive properties. Targeting this pathway may inform a new therapeutic target for improving sepsis outcome.

Biography

Mohamed Elgazzar, PhD, is a Molecular Immunologist and an Associate Professor. He Received his PhD in 2002 from Kumamoto University School of Medicine, Japan. He received his postdoctoral training in Immunology at the National Jewish Medical Center and University of Colorado in Denver and in Infectious Diseases at Wake Forest University School of Medicine in Winston-Salem before joining ETSU. He holds an adjunct assistant professor position in the Department of Biomedical Sciences. He has authored over 36 original research and review manuscripts.

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