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Celastrol inhibits the formation of neutrophil extracellular traps

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Neutrophils are the most abundant leukocytes and provide the front line of defense against invading pathogens. However, neutrophils also contribute to the development of autoimmune diseases. Recent studies suggest that neutrophils and neutrophil extracellular traps (NETs) play an active role in driving the autoimmunity and tissue injury in vasculitis, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA). Thus, inhibition of neutrophil activation and NET formation may provide an effective strategy to prevent and treat autoimmune diseases. Celastrol is a main bioactive compound of anti-rheumatic *Tripterygium wilfordii* extracts (also known as the Thunder God Vine). We found that low concentrations of celastrol can completely inhibit tumor necrosis factor alpha (TNFα) and immune complex-induced neutrophil oxidative burst, and NET formation. In addition, celastrol inhibits the spontaneous release of NET from freshly isolated neutrophils of SLE and RA patients. To elucidate the molecular mechanisms involved in the action of celastrol, we found that treatment of neutrophils with celastrol resulted in decreased phosphorylation of extracellular-signal-regulated kinase (ERK) and NF-kappa-B inhibitor alpha (IκBα), suggesting the involvement of ERK pathway and the transcription factor NF-κB. Furthermore, celastrol treatment also led to decreased citrullination of histone H3, which is essential for chromatin decondensation and NET formation. Collectively, our studies demonstrate a new pathway for the anti-inflammatory function of celastrol and implicate that celastrol-based intervention may be effective for the treatment of different inflammatory and autoimmune diseases involving neutrophils.

Biography

Yangsheng Yu is currently a senior research associate in the Department of Pathology and Microbiology at the University of Nebraska Medical Center. After he obtained his bachelor and doctorate degrees at Nankai University in China, he went to the United States and joined Dr. Kaihong Su's lab as a postdoctoral fellow in 2009. Since then, he has been investigating the potential contribution of V_H replacement to the generation of poly/auto reactive antibodies in systemic lupus erythematosus (SLE), as well as the pathogenic roles of tissue-reactive autoantibodies in SLE organ manifestations. His long term goal is to understand the molecular mechanisms for autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis.

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