Liposomal curcumin (LipocurcTM) and in vitro/in vivo surrogates for cytokine storm associated with uncontrolled EBOLA infection.

Lawrence Helson¹, Peter Sordillo², George Shopp³, Dany Savid³, Annie Bouchard², Walter A. Shaw⁴, Stephen W. Burgess⁵, Burkhard Kloesch⁶, Muhammed Majeed⁷


Abstract

Massive over-production and persistent elevation of inflammatory cytokines over time by the body’s immune system can trigger a dangerous syndrome known as a cytokine storm. Frequently occurs in advanced or terminal stages of Ebola infection. Dysregulation of normal immune response characterized by high levels of circulating cytokines can induce potentially fatal pathologic changes in cells, tissues, and organs leading to multiple organ failure. Uncontrolled Ebola virus (EBOV) infection of peripheral blood mononuclear cells (PBMCs) results in induction of excessive IL-6 and TNF-α production designated as cytokine storm. Important pro-inflammatory cytokines: IL-1β, IL-6, IL-8, and TNF-α.

Curcumin

Suppresses release of IL-1β, IL-8, TNF-α, monocyte chemotactic protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α) from monocytes and macrophages.

Suppresses release of IL-6, IL-8, TNF-α, MCP-1 from monocytes in high-glucose environment.

Curcumin Supresses Release of Other Key Cytokines: IL-2, IL-12, Interferon γ, GROα (CXCL1), GROβ (CXCL2), IP-10 (CXCL10), SDF-1 (CXCL12), IL-5, IL-11, and IL-17.

Curcumin Anti-Viral Activity: HIV-1, HIV-2, HSV, HPV, HTLV-1, HBV, HCV, Japanese encephalitis virus and H1N1 in culture, Hepatitis B in culture.

Materials & Methods

In vitro study

IL-6 and TNF-α production in mouse macrophages: RAW264 cells were pre-incubated for 24h with empty liposomes or LipocurcTM (1-10μM) before being stimulated for 24h with Kdo2-lipid A (10ng/ml) or LPS (100ng/ml). IL-6 and TNF-α release was quantified by ELISA. Cell viability and cell proliferation were analyzed by XTT-assay.

In vivo study

Male Sprague-Dawley (SD) rats (n=8) received empty liposomes or LipocurcTM by gavage 1h prior intraperitoneal (i.p) injection of LPS at 125μg/kg.

Male SD rats (n=8) received empty liposomes or LipocurcTM intravenously (i.v) 5 min prior i.p injection of LPS at 125μg/kg.

Blood samples were taken 2 and 6 h following LPS injection. TNF-α was quantified 2 h post LPS by ELISA. MCP-1, Rantes, MIP-α, IL-1β and IL-6 were quantified 6 h post LPS by ELISA.

Results

In Kdo2-lipid A or LPS-stimulated macrophages, LipocurcTM (5μM) suppressed IL-6 production/release at ~75% (A). Empty liposomes blocked IL-6 to a similar extent (A). TNF-α production was diminished by LipocurcTM at 10μM (B). Empty liposomes showed similar effects at 20μM (B). LipocurcTM up to 5μM did not affect cell growth. Cell viability significantly decreased at 10μM whereas empty liposomes did not negatively influence cell viability (data not shown).

Conclusions

Therapeutic levels of intravenous liposomal curcumin (LipocurcTM) may prevent mortality in patients with Ebola exhibiting signs and symptoms of cytokine storm, and prevent uveitis in patients successfully rehabilitating from the disease.

References