Curcumin, but not mesalamine, inhibits activated T-cells: Implications for combo curcumin-mesalamine UC therapy

Lang A[1], Salomon N[1], Fudim E[1], Picard O[1], Yavzori M[1], Gamus D[1] , Eliakim R[1], Ng SC[2], Ben-Horin S[1]

Gastroenterology Unit, Sheba Medical Center and Sackler School of Medicine, Tel-Aviv University, Israel[1], and Department of Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong[2]

Background and Aims

Curcumin is an active phytochemical compound which has been suggested as a possible efficacious therapy in ulcerative colitis (UC). Mesalamine is an established therapy for UC. Envisioning the potential of combined mesalamine+curcumin for the treatment of UC, we herein investigated the immune inhibition properties of curcumin and mesalamine alone and in combination

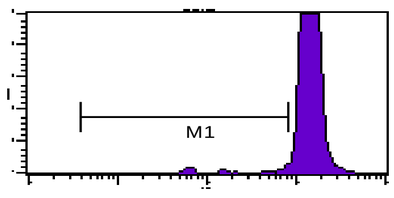
Methods

Curcumin (Bara Herbs Inc, Hazorea, Israel) and Mesalamine (Sigma, Israel) were dissolved in DMSO and added in graded concentrations to peripheral blood mononuclear cells (PBMC) from healthy volunteers. Effects of the drugs alone or in various combinations on anti-CD3 stimulated CD4+ T- cells proliferation and apoptosis were investigated by CFSE dilution FACS analysis. The secretion of TNF-alpha and IL-8 from stimulated PBMC was assessed by ELISA.

Results

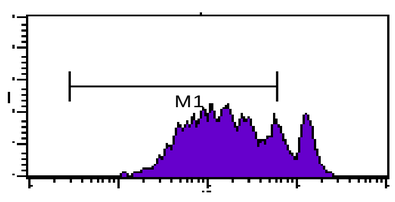
Curcumin at a concentration of 5μM abrogated CD+ T-cell proliferation by 48%±19% compared to vehicle alone, but without a discernable effect on apoptosis induction. Pro-inflammatory cytokine secretion was inhibited by curcumin in a dose-response fashion. Curcumin at 5mM significantly reduced TNF-alpha secretion from anti CD-3 stimulated peripheral blood PBMC (1400±224 vs. 369±165 pg/ml, p<0.01) andIL-8 secretion (1605±153 vs. 354±146 pg/ml, p=0.01). In contrast, mesalamine at different doses did not inhibit T-cell proliferation, cytokine secretion or cell survival. Combining mesalamine in graded concentrations with curcumin produced similar findings as observed with curcumin alone.

Medium



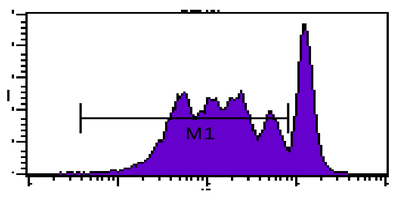
Marker	% Gated	% Total
All	100.00	58.95
M1	1.51	0.89

T3



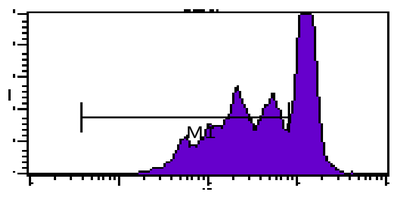
Marker	% Gated	% Total
All	100.00	18.45
M1	82.02	15.13

Okt3 + curcumin 2.5uM



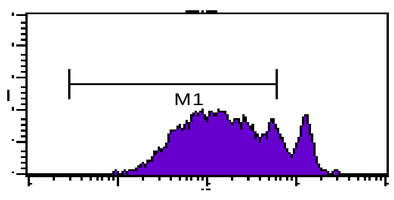
Marker	% Gated	% Total
All	100.00	60.23
M1	75.36	45.39

Okt3 + curcumin 5uM



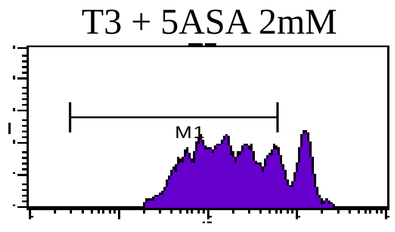
Marker	% Gated	% Total
All	100.00	49.83
M1	56.89	28.35

T3 + 5ASA 0.5mM



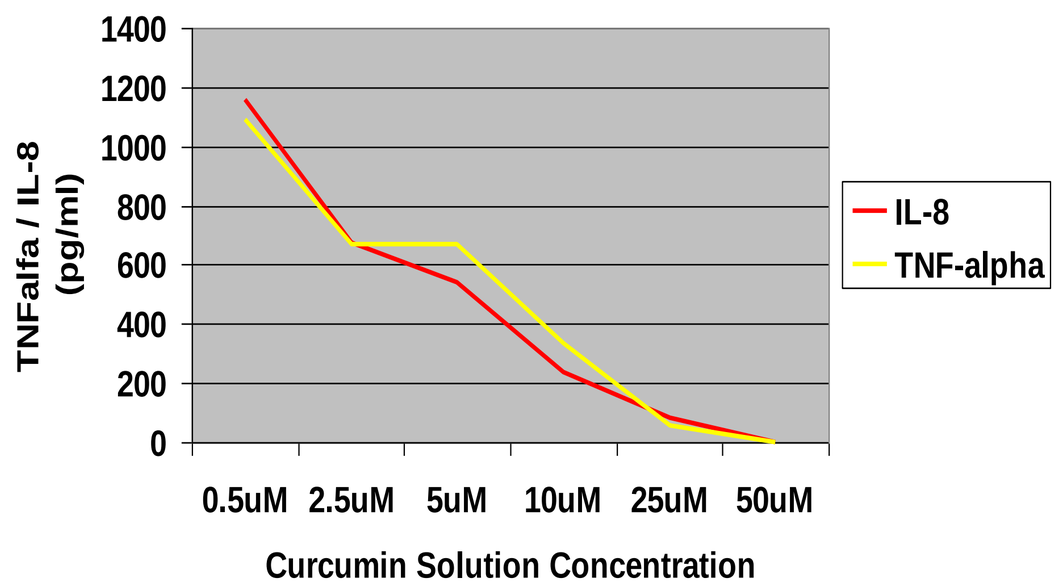
Marker	% Gated	% Total
All	100.00	17.58
M1	83.96	14.76

T3 + 5ASA 2mM

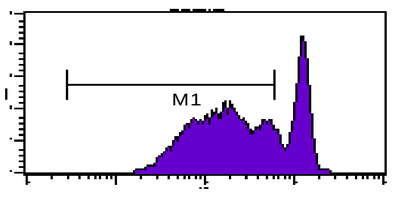


Marker	% Gated	% Total
All	100.00	17.67
M1	79.95	14.13

Dose related reduction of TNF-alpha and IL-8 secretion by curcumin

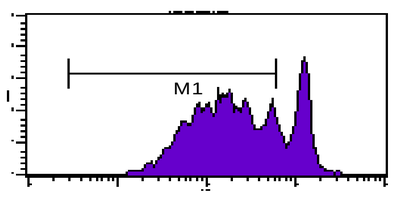


T3 + Curcumin 2.5uM+5asa0.5mM



Marker	% Gated	% Total
All	100.00	17.93
M1	76.08	13.64

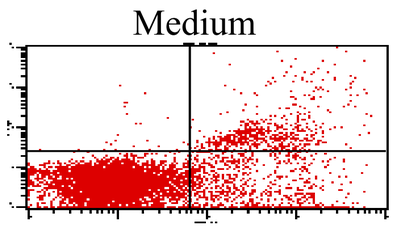
T3 + Curcumin 2.5uM+5asa 2mM



Marker	% Gated	% Total
All	100.00	17.50
M1	72.96	12.77

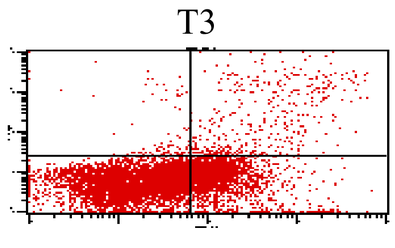
No discernable difference between apoptosis rate of Cd+ T cells exposed to curcumin comapred to stimuation with T3 alone

Medium



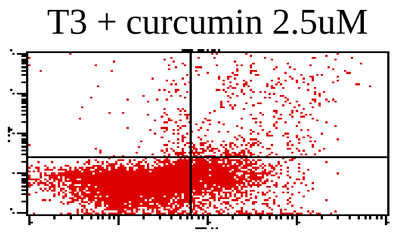
Quad	% Gated	% Total
UL	0.35	0.21
UR	8.06	4.93
LL	80.07	49.01
LR	11.53	7.06

T3



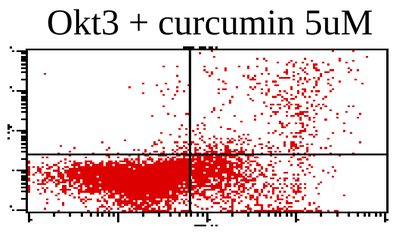
Quad	% Gated	% Total
UL	1.20	0.81
UR	5.08	3.43
LL	68.94	46.56
LR	24.78	16.74

T3 + curcumin 2.5uM



Quad	% Gated	% Total
UL	2.03	1.28
UR	5.90	3.73
LL	69.83	44.18
LR	22.24	14.07

Okt3 + curcumin 5uM



Quad	% Gated	% Total
UL	1.29	0.74
UR	7.08	4.05
LL	76.42	43.69
LR	15.20	8.69

Conclusions

Curcumin exerts inhibitory effects on immune activation which are not mediated by apoptosis induction. These immuno modulatory effects are not produced by the 5-aminosalicylate compound mesalamine. Given the proven efficacy of mesalamine in the treatment of UC, combining mesalamine with curcumin in vivo may allow a dual-hit mechanism of action, and a clinical trial to investigate this approach in patients with UC is now on-going.