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Title: COPD monocytes differentiate into pro-inflammatory macrophages regardless of environment

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Body: COPD is a chronic inflammatory lung disease associated with an increased pro-inflammatory macrophage (mϕ) response whereby cells produce increased pro-inflammatory mediators CXCL8 and TNFα and decreased anti-inflammatory mediator IL-10. A monocyte-derived macrophage (MDM) model was used to study the effect of adherence and fetal calf serum (FCS) on mϕ phenotype in non-smokers (NS n=3), smokers (S n=3) and COPD patients (COPD n=3). Monocytes were isolated and cultured for 12d in either adherent or non-adherent plates in the presence or absence of FCS and addition of either GM-CSF (G-mϕ, M1) or M-CSF (M-mϕ, M2). MDM were stimulated for 24h with either LPS or IL-4 and levels of CXCL8, TNFα and IL-10 measured by ELISA. Baseline cytokine production was minimal and did not differ between groups. G-mϕ from COPD patients stimulated with LPS produced significantly more TNFα and CXCL8 compared to NS and S (Table 1).

ng/ml	NS	S	COPD
CXCL8	114±47	182±39	317±88
TNFα	14±6	14±5	30±9

LPS-stimulated cytokine release

This persisted when G-mϕ were cultured without serum or adherence. Lower levels of cytokines were released by M-mϕ, although COPD MDM remained pro-inflammatory. M-mϕ from S and COPD patients stimulated with IL-4 released less IL-10 than cells from NS (Table 2). This effect was lost in FCS-free media.

ng/ml	NS	S	COPD
IL-10	2.1±0.2	0.2±0	0.6±0.5

IL-4-stimulated IL-10 release

COPD MDM consistently produce more pro-inflammatory cytokines and less IL-10 regardless of culture

condition. FCS may be priming MDM to produce more cytokines when stimulated ex-vivo. These data suggest that circulating monocytes are primed in patients with COPD to generate a pro-inflammatory mϕ regardless of environment.