**Figure S1**

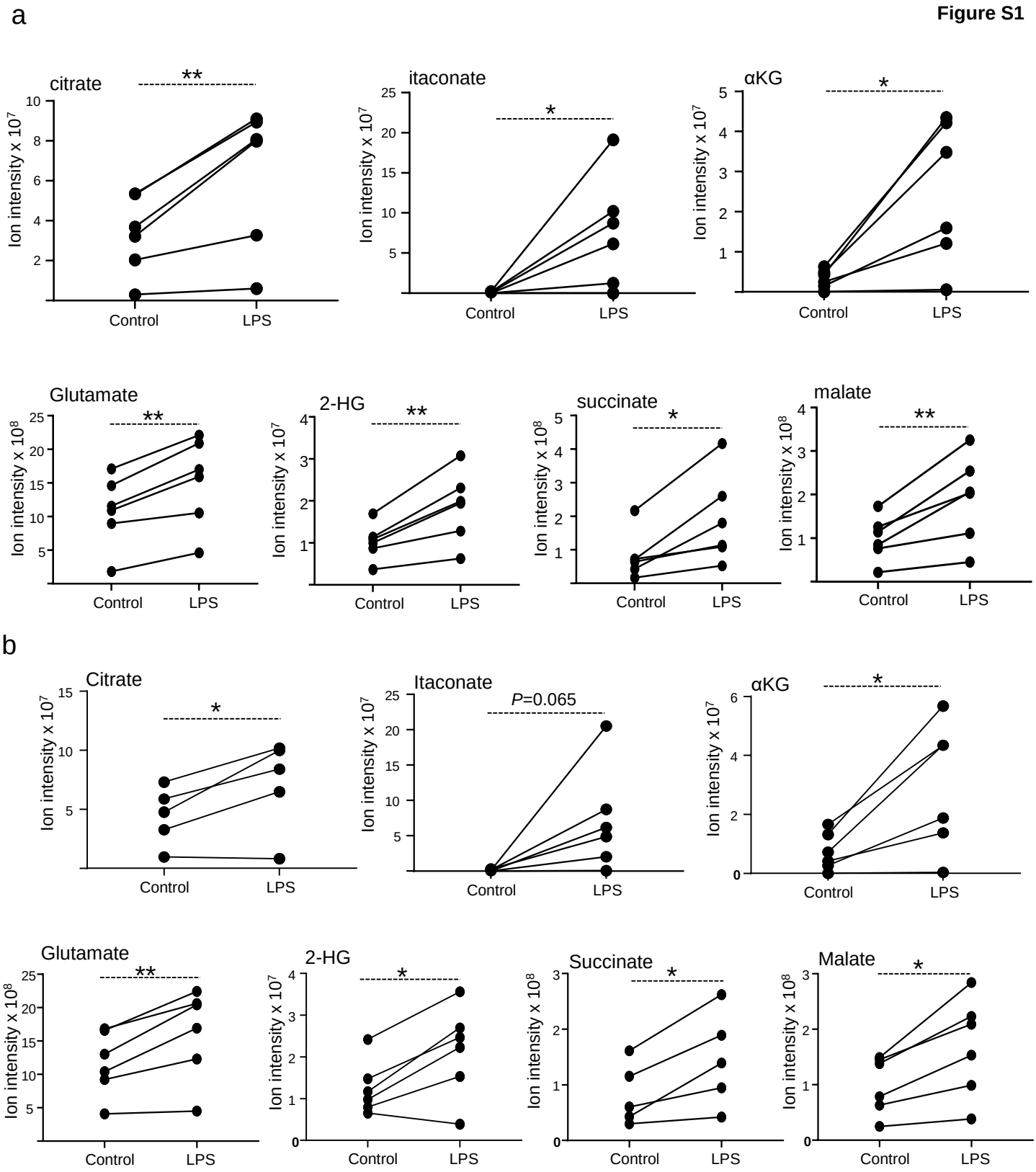


**Figure S1**. Early LPS activation increases the TCA cycle volume in human macrophages. LC-MS for itaconate, TCA cycle and αKG-derived metabolites in control and LPS (8 hours)-treated hMDMs incubated either with [U-$^{13}$C]-glucose (**a**) or [U-$^{13}$C]-glutamine (**b**). Data points are the sum of M+0 and glucose (**a**) or glutamine-derived (**b**) isotopologues; n=6 donors; significance was tested with paired t-test. *, P<0.05; **, P<0.01.

**Figure S2**

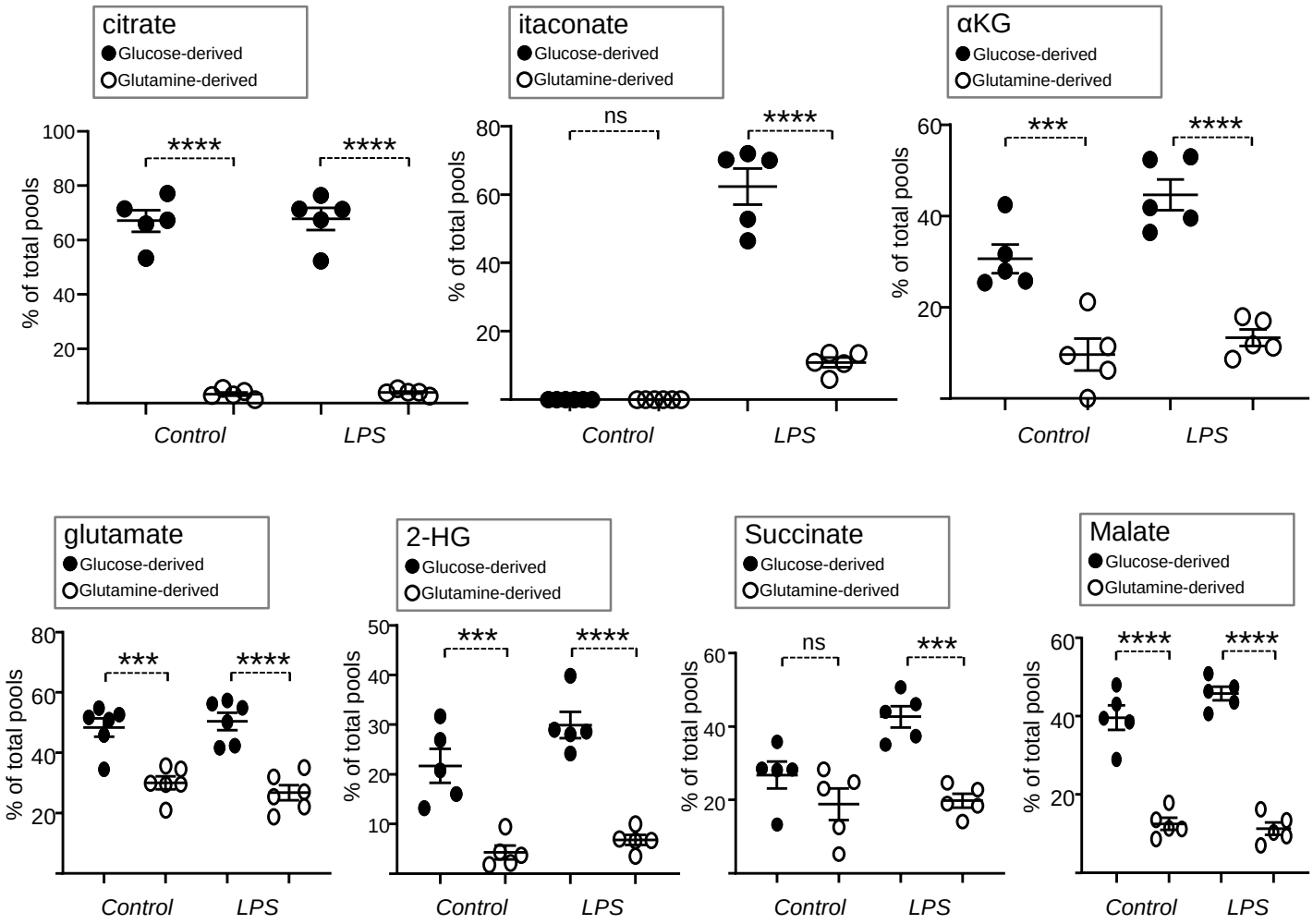


**Figure S2**. Glucose but not glutamine is a major contributor of the early increase in TCA cycle activity in human macrophages. LC-MS showing the glucose and glutamine-derived isotopologues (as percentage of total pools of metabolites) in control and LPS (8 hours)-treated hMDMs incubated either with [U]-$^{13}$C-glucose (black circles) or with [U]-$^{13}$C-glutamine (open circles) ; at least n=5 donors and significance was tested with one-way ANOVA followed by Tukey test; ***, P<0.001; ****, P<0.0001; ns, non-significant.

**Figure S3**

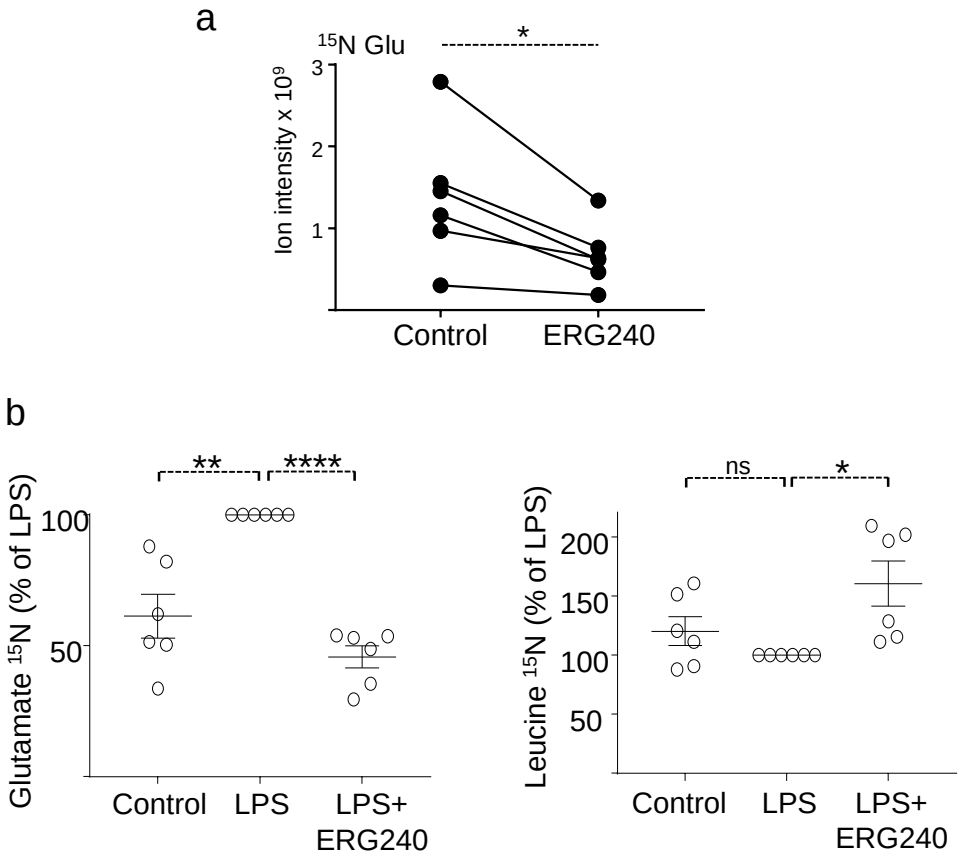


**Figure S3**. The leucine analogue ERG240 inhibits BCAT1 transamination activity and rescues its LPS-dependent up-regulation. **a**. LC-MS for [$^{15}$N]-Glutamate in [$^{15}$N]-Leucine incubated hMDMs in basal and ERG240-treated conditions. **b**. [$^{15}$N]-Glutamate and [$^{15}$N]-Leucine levels in basal (Control), LPS (8 hours; 100ng/ml) and LPS+ERG240 (8 hours) treatment conditions following incubation with [$^{15}$N]-Leucine; n=6 donors and significance was tested with paired t-test (**a**) or by one sample t test (**b**); *,P<0.05; **, P<0.01; ****, P<0.0001; ns, non-significant.

**Figure S4**

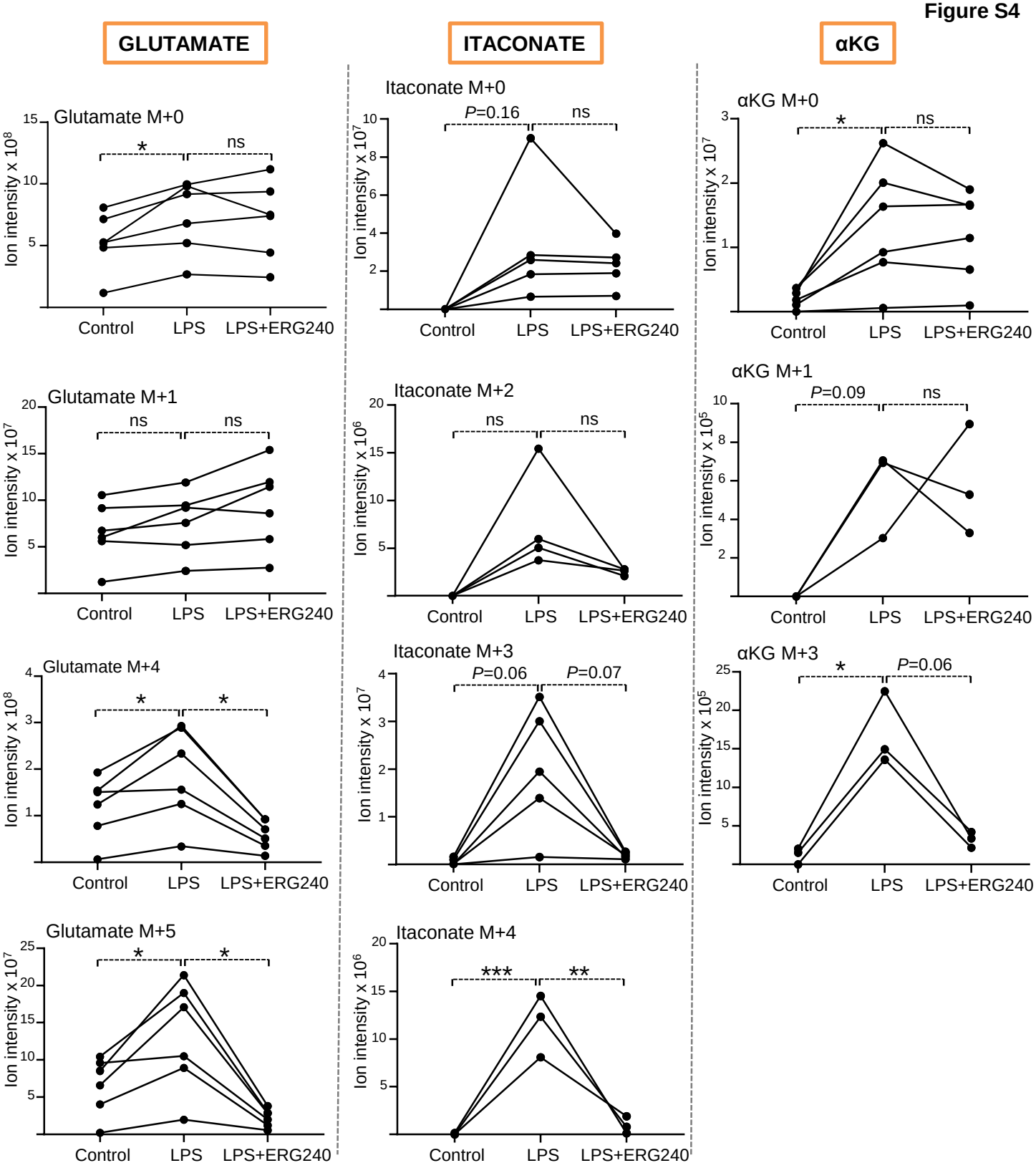


**Figure S4**. BCAT1 inhibition affects glucose-derived itaconate, αKG and glutamate levels in human macrophages. LC-MS for M+0 and glucose-derived glutamate (left column), itaconate (middle column) and αKG (right column) isotopologues in control (basal), LPS (8 hours) and LPS+ERG240 (8 hours)-treated hMDMs; at least n=3 donors; significance was tested with paired ANOVA followed by Tukey's test. *, P<0.05, **, P<0.01; ***, P<0.001; ns, non-significant.

**Figure S5**

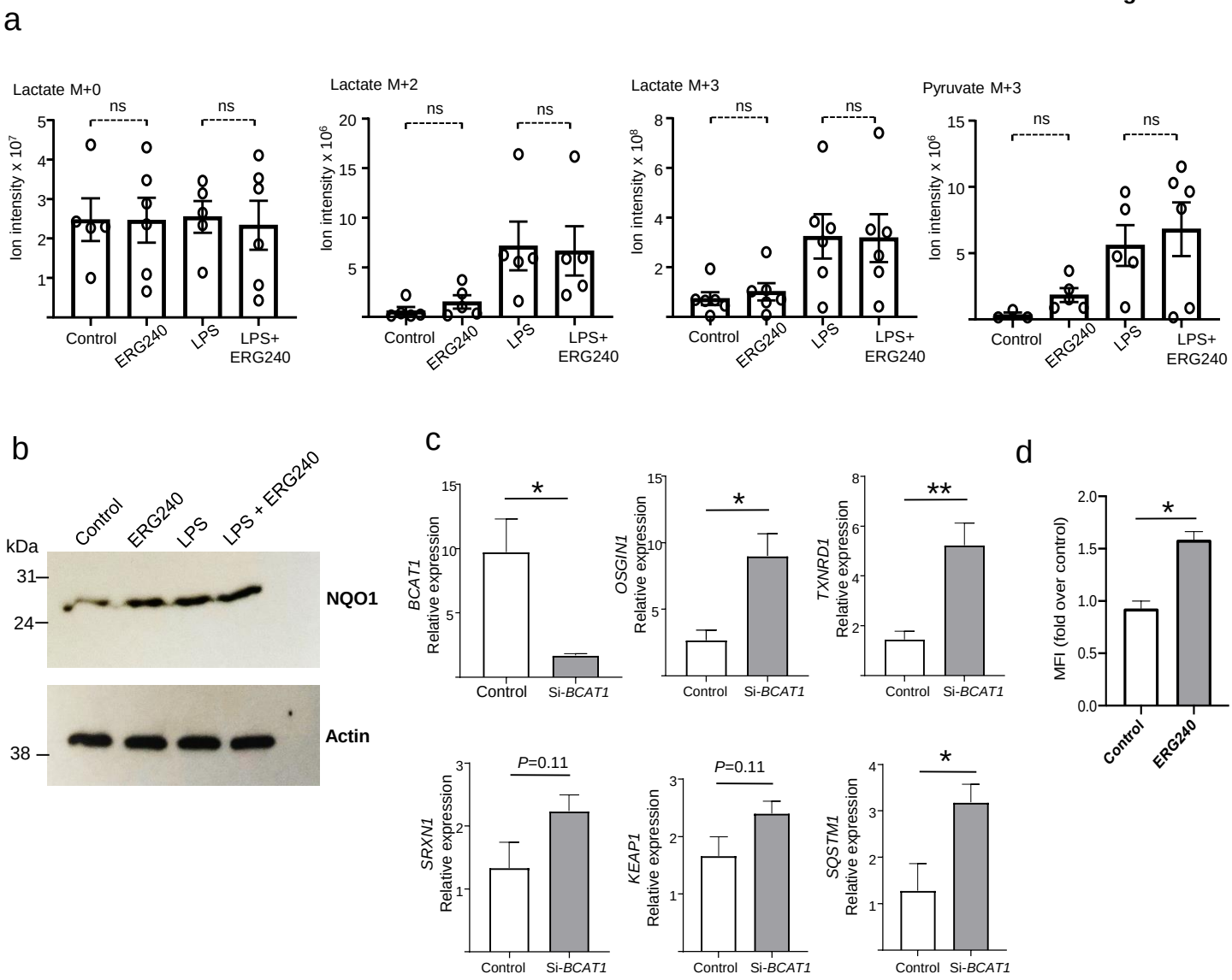


**Figure S5**. The effect of BCAT1 inhibition on glycolysis and NRF2 pathway in human macrophages. **a**. LC-MS for Lactate M+0, Lactate M+2, Lactate M+3 and Pyruvate M+3 in control (Ctrl), LPS (8h; 100ng/ml), ERG240 and LPS+ERG240-treated hMDMs. **b**. NQO1 Western Blot in control, ERG240, LPS and LPS+ERG240-treated hMDMs. **c**. qRT-PCR for *BCAT1* and NRF2 targets following *BCAT1* siRNA (si-*BCAT1*) or scrambled control (Control). The relative expression levels were normalized to *HPRT* expression levels. **d**. hMDMs were left untreated (Control) or treated 30 min with ERG240. Live cells were analysed by FACS and mean fluorescence intensity (MFI) was quantified as a measure of mitochondrial ROS production. (**a**); at least n=3 donors; significance was tested with one-way ANOVA followed by Tukey's test. (**b**) – (**d**); N=2 donors; significance was tested by t-test. *, P<0.05; **, P<0.01; ns, non-significant.