

Title: BLR1 and FCGR1A transcripts in peripheral blood associate with the extent of intrathoracic tuberculosis in children and predict treatment outcome.

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Supplementary Table 1. Transcriptional markers measured direct ex-vivo showing significant fold change from baseline to 2 months on treatment in the four micronutrient intervention groups **(A)**. Proteomic markers measured direct ex-vivo showing significant fold change from baseline to 2 **(B)** and 6 months **(C)** on treatment in the four micronutrient intervention groups. Blank field means no significant change. 95% confidence intervals are given in parentheses.

A				
	MN+Zn	MN	Zn	Placebo
N baseline	23	18	23	24
N 2 months	13	15	18	19
<i>ABR</i>			1,23 (1,03-1,47)	
<i>B2M</i>		0,69 (0,60-0,79)	0,77 (0,68-0,88)	
<i>BCL2</i>	1,79 (1,36-2,34)	1,77 (1,36-2,29)	1,54 (1,22-1,94)	1,9 (1,51-2,38)
<i>BLR1</i>	2,63 (1,60-4,31)	1,94 (1,20-3,14)	2,26 (1,47-3,46)	1,97 (1,29-3,00)
<i>CASP8</i>	1,46 (1,21-1,76)	1,11 (0,93-1,33)	1,21 (1,03-1,42)	1,25 (1,07-1,47)
<i>CCR7</i>	1,56 (1,14-2,13)		2,09 (1,59-2,74)	1,32 (1,01-1,72)
<i>CD14</i>	0,41 (0,28-0,59)			
<i>CD19</i>	1,74 (1,22-2,48)	1,47 (1,00-2,16)	2,4 (1,73-3,33)	2,41 (1,75-3,30)
<i>CD3E</i>	1,93 (1,41-2,64)	2,01 (1,48-2,72)	1,76 (1,34-2,31)	1,96 (1,5-2,56)
<i>CD4</i>	1,46 (1,04-2,05)	1,43 (1,04-1,99)	1,79 (1,34-2,41)	1,47 (1,1-1,96)
<i>CD8A</i>				0,39 (0,15-0,99)
<i>FCGR1A</i>	0,43 (0,29-0,63)	0,51 (0,35-0,75)	0,52 (0,37-0,72)	0,71 (0,51-0,99)
<i>FOXP3</i>		0,009 (0,00-0,94)	0,004 (0,00-0,39)	
<i>FPR1</i>	0,63 (0,51-0,78)	0,74 (0,60-0,91)	0,78 (0,65-0,93)	0,76 (0,63-0,91)
<i>GUSB</i>		1,35 (1,07-1,70)	1,58 (1,29-1,95)	1,23 (1,00-1,51)
<i>IL7R</i>	1,83 (1,41-2,36)	1,54 (1,20-1,99)	1,46 (1,17-1,82)	1,57 (1,26-1,96)
<i>LTF</i>				0,46 (0,33-0,64)
<i>MARCO</i>				0,69 (0,49-0,96)
<i>MMP9</i>	0,25 (0,14-0,45)	0,55 (0,32-0,93)	0,44 (0,26-0,74)	0,22 (0,13-0,37)
<i>NCAM1</i>			1,74 (1,30-2,32)	
<i>RAB24</i>	0,68 (0,47-0,96)	0,71 (0,51-0,99)		
<i>SEC14L1</i>			1,28 (1,01-1,62)	
<i>TGFB1</i>			1,23 (1,02-1,48)	
<i>TGFBR2</i>	1,51 (1,26-1,81)	1,26 (1,06-1,50)	1,38 (1,18-1,62)	1,2 (1,03-1,40)
<i>TIMP2</i>	0,75 (0,65-0,87)			
<i>TNFRSF1B</i>			1,72 (1,27-2,33)	

B				
	MN+Zn	MN	Zn	Placebo
N baseline	23	18	23	24
N 2 months*	13	15	18	19
IFN α -2	0,57 (0,38-0,85)	0,57 (0,40-0,82)	1,41 (1,04-0,82)	
IFN γ		0,46 (0,28-0,73)	0,48 (0,32-0,73)	0,38 (0,25-0,6)
IL12p70		0,49 (0,25-0,98)		
IL-13	4,46 (2,03-9,81)		2,10 (1,02-4,32)	
IL-17A		0,54 (0,32-0,93)	0,73 (0,54-0,99)	
IL-1 β			0,35 (0,16-0,74)	
IL-2		0,40 (0,20-0,78)	0,37 (0,21-0,66)	0,39 (0,21-0,72)
IL-5			2,07 (1,21-3,52)	
IP-10			0,69 (0,53-0,91)	
MCP3	2,73 (1,35-5,50)			

C	
	Placebo
N baseline	24
N 6 months	10
IFN α -2	
IFN γ	0,38 (0,24-0,62)
IL12p70	
IL-13	
IL-17A	0,34 (0,21-0,56)
IL-1 β	
IL-2	0,30 (0,14-0,65)
IL-5	
IP-10	0,59 (0,43-0,80)
MCP3	

% fold decrease	
	≤30
	>30, ≤50
	>50, ≤70
	>70, ≤90
	>90, ≤200
	>200

% fold increase	
	≤30
	>30, ≤50
	>50, ≤70
	>70, ≤90
	>90, ≤200
	>200

Supplementary Table 2: Genes investigated in the dcRT-MLPA and their functions. The table has been modified from table previously published by the same authors.¹

Genes	Putative role	Reference	Method for biomarker discovery ²
BCL2	B-cell lymphoma 2, down-regulates cell death (apoptosis). Increased <i>BCL2</i> expression in infected macrophages may create an immune privileged site for MTB infection and is implicated in poor prognosis for TB patients.	3,4	A, C
BLR1	Belongs to CXC chemokine receptor family (CXCR5), located in lymph node follicles. An increased expression of <i>BLR1</i> in TB patients might help in sustaining the expression of its ligand CXCL13, which in turn attracts B cells.	5	C
BPI	Bactericidal permeability-increasing protein, found in neutrophil granules and associated with host defence through microbiocidal activity.	6	C
CASP8	Cysteine-aspartic acid protease family, plays a central role in the execution-phase of cell apoptosis and increased expression is seen in TB patients	7,8	C
CCL4	Chemokine (c-c motif) ligand 4 or Macrophage inflammatory protein 1 β (MIP-1 β), acts as chemo-attractant for a variety of immune cells.	9	C
CCL13	Chemokine (c-c motif) ligand 13, link immune activation to the recruitment of leukocytes in both Th1-and Th2-type immune responses.	10	B,C
CCL19	Chemokine (c-c motif) ligand 19, contributes to control of MTB infection through homing of lymphocytes and dendritic cells.	11	B
CCL22	Belongs to CC chemokine family, plays a role in the trafficking of activated T cells to inflammatory sites.	9	C
CCR7	CC chemokine receptor 7, mediates trafficking of dendritic cells and T cells from the lungs to the mediastinal lymph node during TB disease.	12,13	C
CD3E	T-cell glycoprotein CD3 epsilon, plays a role in intracellular signal-transduction pathways.	14	C
CD4	Cluster of differentiation 4, plays a critical role in adaptive immunity to TB.	2	C
CD8A	Cluster of differentiation 8A, identifies cytotoxic T- cells that interact with MHC class I targets and may contribute to control of MTB infection.	15	C
CD14	Cluster of differentiation 14, a component of the innate immune system and acts a co-receptor for recognizing MTB. Monocyte/macrophage marker.	16,17	C
CD19	Cluster of differentiation 19, a B cell marker and essential for B cell activation.	18	C
CD163	Cluster of differentiation 163, a hemoglobin scavenger receptor exclusively expressed in macrophages upon inflammation.	19	C
CTLA4	Cytotoxic T-lymphocyte antigen 4 plays a role in the down-regulation of T cell immune responses and involved in the maintenance of T cell homeostasis. <i>CTLA4</i> gene expression may be associated with severity of pulmonary TB.	20,21	B,C
CXCL10	CXC chemokine 10 or interferon gamma-induced protein 10 (IP-10), secreted by number of cell types in response to IFN- α/β and involved in stimulation of natural killer cells and T-cell migration in MTB infection.	22	A, C
FASLG	Fas ligand, a type II transmembrane protein, belonging to the TNF family involved in immune modulation and pathogenesis of TB. Modulators of Fas/FasL-mediated apoptosis may therefore be clinically useful.	23	C

FCGR1A	The Fc region of immunoglobulin gamma is involved in both innate and adaptive immune responses. It aids to control MTB infection and plays a central role in antibody-dependent cytotoxicity and the clearance of immune complexes.	24	C
FOXP3	Forkhead box P3, belongs to the transcription factor family and is involved in various cellular processes, acts as an important regulator for T-cell development.	25	C
FPR1	Formyl peptide receptor 1, a member of G-protein-coupled receptor family involved in the control of inflammation and neutrophil function.	26	C
IFNγ	Interferon gamma, secreted by several cell types such as NK cells, CD4 ⁺ and CD8 ⁺ T-cells, essential for control of MTB infection.	27	B
IL2RA	Interleukin 2 receptor gene, plays an important role in the activation and expansion of T-cells.	28	C
IL4	Interleukin 4, the prototypical Th2 cytokine; high levels of expression are associated with poor outcomes in TB.	29	C
IL4d2	IL-4 antagonist and splice variant of interleukin-4.	30	C
IL7R	Interleukin-7 receptor, plays a role in the development of immune cells and control of apoptosis.	31	C
IL10	Interleukin-10, an anti-inflammatory cytokine that may contribute to TB pathogenesis. IL-10 blocks phagosome maturation by a STAT3-dependent, p38-independent mechanism, which facilitates MTB survival and outgrowth	32	A
IL22RA1	Interleukin 22 receptor alpha 1 belongs to class II cytokine receptor family and activates various signaling pathways. The expression of <i>IL22RA1</i> was found to be higher in late TB granulomas.	33,34	B
LAG3	Lymphocyte-activation gene 3, an important regulatory molecule involved in controlling the expansion and activation of T-cells.	35	A,C
LTF	Lacto-transferrin also called Lactoferrin (LF), a secreted mediator that connects innate and adaptive immune responses.	36	C
MARCO	Antigen-presenting cell scavenger receptor, involved in TLR activation that mediates phagocytosis of pathogens.	37	C
MMP9	Matrix metallo-peptidase 9, induced by MTB infection and has a role together with MCP-1 in recruiting macrophages to the lungs during granuloma formation.	38	C
NCAM1	Neural cell adhesion molecule 1, mediates several intracellular signaling pathways and may be involved in TB pathogenesis.	39,40	A
RAB13	Ras related protein-13, a small GTPase family member, regulates assembly of functional tight junctions in epithelial cells.	41	C
RAB24	Ras related protein-24, a small GTPase family member, regulates intracellular protein trafficking between endoplasmic reticulum and cis-Golgi compartment.	41	C
RAB33A	Ras related protein-33A, a small GTPase family member; Dysregulation of GTPase plays a role in blocking of phagosome maturation, which is a major survival strategy for MTB.	42	C
SEC14L1	SEC14 cytosolic factor family plays a role in lipid metabolism and the intracellular transport system. SEC14L1 also appears to be a negative regulator of some innate immune functions.	43,44	C
SPP1	Secreted phosphoprotein 1, acts as a cytokine that up-regulates the expression of interferon-gamma and interleukin-12, contributes to resistance against mycobacteria by boosting reactive oxygen intermediate production in macrophages.	45,46	C
TGFB1	Transforming growth factor β 1, an anti-inflammatory cytokine, performs many cellular functions and is involved in resolution of granulomatous lesions in TB.	47	C

TGFBR2	Transforming growth factor β receptor 2, involved in signal transduction and response to inhibit cell growth and division.	48	C
TIMP2	Tissue inhibitor of metallo-proteinases, involved in pathological changes, tissue remodeling and possibly, pathogenesis of pulmonary TB.	49	C
TNF	Tumor necrosis factor, a cytokine that plays multiple roles in the immunopathology of TB and is essential for controlling MTB infection.	50	B, C
TNFRSF1A	TNF receptor superfamily member1A, mediates apoptosis and functions as a regulator of inflammation.	51	C
TNFRSF1B	TNF receptor superfamily member 1B, mediates anti-apoptotic signals.	51	C
TNFRSF18	TNF receptor superfamily member 18, involved in T-cell activation, programmed cell death and pulmonary fibrosis.	49,51	C
ABR	Active BCR-Related gene contains a GTPase-activating protein domain (used as endogenous control).		
B2M	β 2 microglobulin, a component of MHC class I molecules (used as endogenous control).		C
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase, involved in quite a few non-metabolic processes (used as endogenous control).		
GUSB	Glucuronidase β , regulates lysosomal storage function and co-regulated in response to stress (used as endogenous control).	52	

(A) Experimental in vitro studies, (B) Experimental in vivo studies, (C) ELISA/ELISPOT/Microarray/qPCR on clinical samples.

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