PBMC TRANSCRIPTOME REVEALED A BENEFICIAL IMMUNE ACTIVATION AGAINST HIV-1 IN LGMD1F

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BACKGROUND

TNPO3 is an importin involved in nuclear transport of splicing factors and HIV capsid. LGMD1F (currently designated as LGMDD2) is a rare genetic muscle disease characterized by a heterozygous deletion in TNPO3 gene, which generates an isoform with 15 additional amino acids.

Our previous studies in 32 individuals affected by LGMD1F demonstrated that cells from these patients are resistant to HIV-1 infection *in vitro* through interference with viral integration.

METHODS

- Peripheral blood mononuclear cells (PBMC) from 20 participants were isolated, including 10 individuals affected by LGMD1F (asymptomatic, mild-symptoms and severe-symptoms) and 10 non-affected relatives.
- RNA-Seq libraries were sequenced in a NextSeq 550 platform (Illumina).
- Plasma levels of IFN-β and IFN-γ were measured by a Luminex assay (R&D Systems).
- Full-length HIV clone and VSV-pseudotyped infections were assessed in PBMC activated with CD3+CD28+IL2. Expression of MxA in infected lymphocytes was determined by flow cytometry.

The study suggests a basal immune activation mediated by **interferons** and a **pro-inflammatory state** in LGMD1F patients, characterized by the alteration of **IL-17 signaling pathway** and the consequent increase of **metalloprotease activity** and **TNF response**.

The increase in interferons and inflammatory mediators suggests an antiviral environment and **resistance to HIV-1 infection**, but also could **impair muscular function** in LGMD1F patients, **worsening disease evolution**.

Biomarkers of disease progression and **therapeutic strategies** based on these mechanisms should be further investigated for this type of **muscular dystrophy**.

RESULTS

CONCLUSIONS

The present study gives a new perspective of LGMD1F pathology, providing new actors implicated in this muscular dystrophy, such as IL-17, metalloproteases, cytokines TNF and IL-1β, and interferons.

These findings suggest that TNPO3 mutation, either directly or through muscular damage, provokes changes in gene expression that increase basal immune activation in LGMD1F patients. On one hand, this inflammatory state can be harmful and contribute to muscular damage. But on the other hand, increased IFN activity confers an additive mechanism in restraining HIV-1 infection apart from the direct impact of TNPO3 in capsid transport and HIV integration.

ACKNOWLEDGEMENTS

"Conquistando Escalones" the association of patients affected with LGMD1F

Table 1. Clinical characteristics of LGMD1 patients.

ID	Gender (male/female)	Age at onset	Proximal weakness/ atrophy	Distal weakness/ atrophy	Brooke scale	Vignos scale
III.1	female	-	-	-	1	0
III.12	male	40	SH, PF	HAW/LW	3	6
IV.1	male	-	-	-	-	0
IV.26	male	5	SH, PF	HA/LW	4	7
IV.29	female	7	SH, PF	HA/LW	2	3
IV.31	female	18	SH, PF	HAW/LW	2	4
V.1	male	12	PF	-/LW	4	4
V.2	female	3	PF	HA/LWA	4	4
V.30	female	1	SH, PF	HA/LW	3	4
V.36	female	1	PF	HA/LW	1	3

SH: scapular-humeral; PF: pelvic-femoral; HAW: hand atrophy and weakness; LW: leg weakness; HA: hand atrc
not avaible

Figure 1. Differentially expressed genes with higher FC between LGMD1F patients and their non-affected relatives.

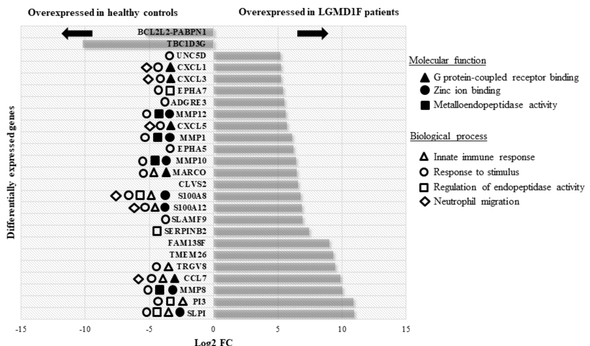

Figure 2. Enriched pathways of KEGG database associated to differentially expressed genes between LGMD1F patients and their non-affected relatives.

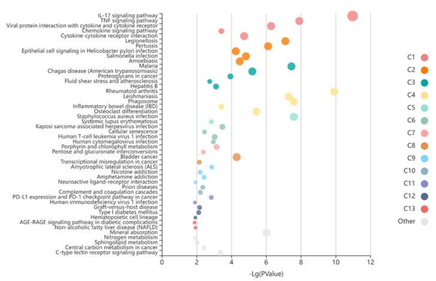

Figure 3. Increased metallopeptidases expression (MMP1, MMP8, MMP9, MMP10, MMP12, and MMP14) in LGMD1F patients.

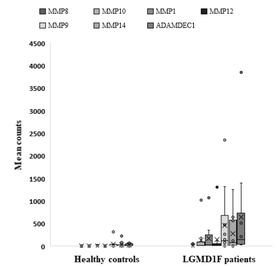

Figure 4. Inflammatory response in LGMD1F patients evidenced by altered IL-17 (A) and TNF (B) signaling pathways.

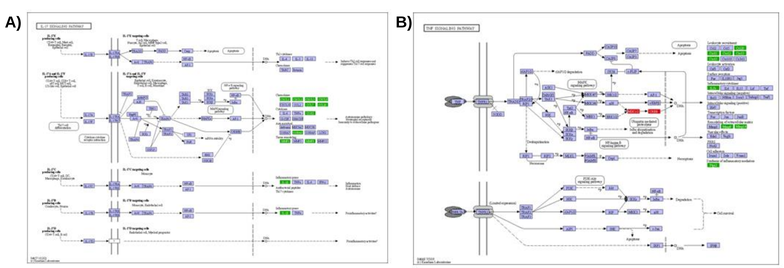

Figure 5. Several genes of Toll-like receptors (TLR) and NF-κB signaling pathways were differentially expressed between LGMD1F patients.

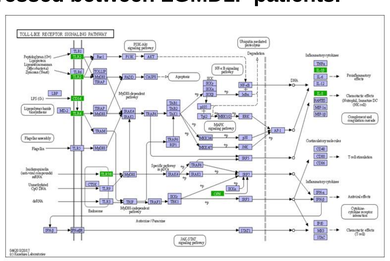

Figure 6. Increased IFN-β (A) and IFN-γ (B) production in plasma samples from healthy controls and LGMD1F patients.

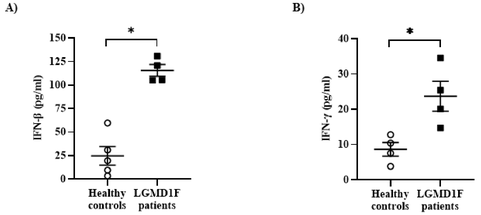

Figure 7. HIV-1 infection in vitro triggers higher levels of MxA (an IFN-stimulated gene) in lymphocytes.

