

BTK mutation affects cytokine production after viral RNA recognition in myeloid dendritic cell

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Dendritic cells

- antigen presenting cells
- stimulation of naive T cells
- Toll-like receptors

Bruton's tyrosin kinase

- protein in B cells development
- mutation – lack of B cells and antibodies
 - Bruton's agammaglobulinaemia, X-linked agammaglobulinaemia
- Jefferies 2003 – btk in TLR signaling
(TLR4, TLR6, TLR7, TLR8)

Does the mutation in btk affect TLR signaling and DC function?

- all TLR with known ligands investigated

TLR2	Zymosan, LTA,
TLR6	Peptidoglycan
TLR3	Poly(I:C)
TLR4	Lipopolysaccharide
TLR5	Flagellin
TLR7	Loxoribine, ssRNA
TLR8	ssRNA
TLR9	CpG

Investigated cells

DC obtained from:

- X-LA patients
- healthy donors
- healthy donors - pretreated 1h before TLR stimulation with specific btk inhibitor – LFM-A13 (25uM / 100 uM)

Conclusion ESID 2005

- **Mutation in btk does not influence:**
 - **phenotype**
 - **endoocytic activity**
 - **potential to stimulate T cell**
 - **IL-12 production**

**in myeloid dendritic cells after TLR
stimulation**

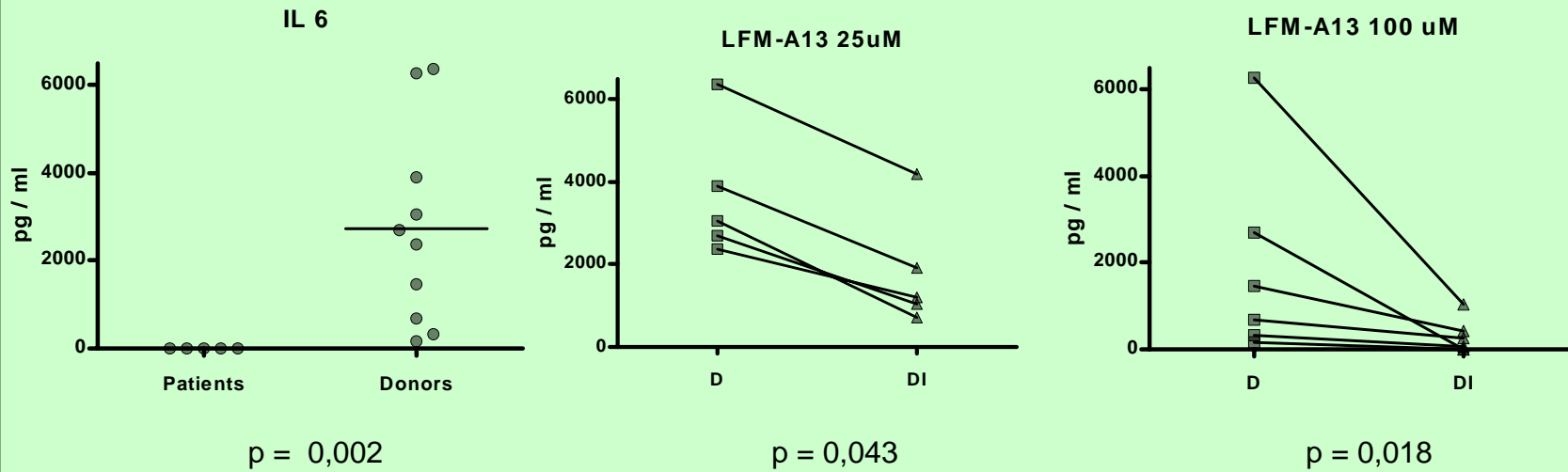
Cytokine production

IL-8, IL-10 – no effect of *BTK* mutation

IL-6, TNF – no difference among 3 investigated group after
TLR 2, 3, 4, 5, 6 stimulation

- TLR 8 stimulation (ssRNA) – impaired production

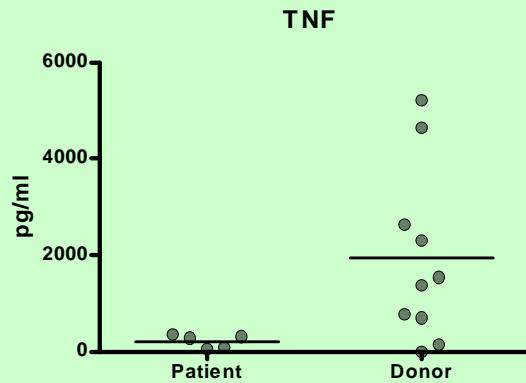
IL-6 production after ssRNA stimulation



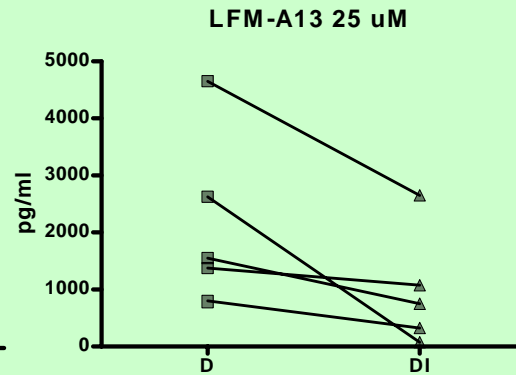
D – healthy donor without inhibition

DI – healthy donor pretreated with specific inhibitor of btk

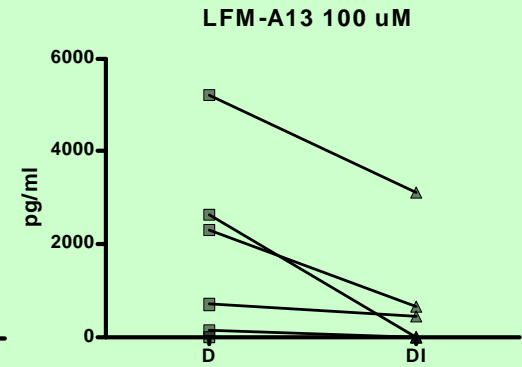
TNF production after ssRNA stimulation



$p = 0,028$



$p = 0,043$

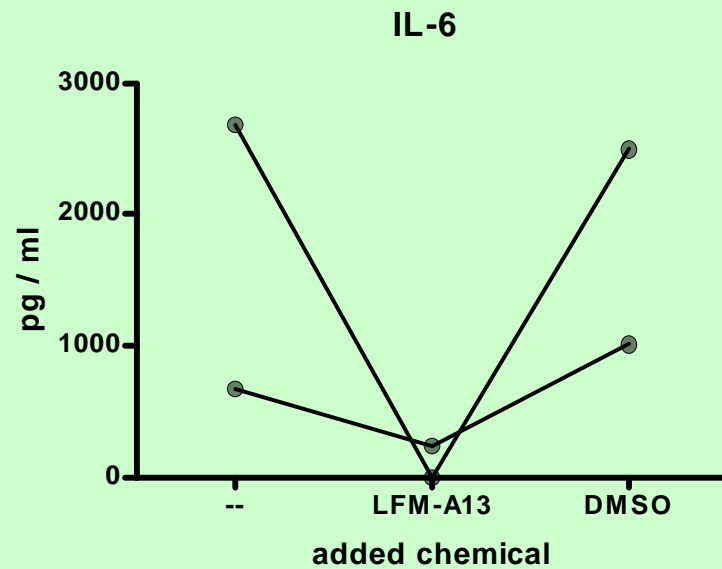


$p = 0,043$

D – healthy donor without inhibition

DI – healthy donor pretreated with specific inhibitor of btk

The influence of DMSO - solvent of LFM-A13



Conclusion

- TLR7 and TLR9 not expressed on myeloid DC – no maturation of DC
- no influence of BTK mutation on DC phenotype, endocytic activity and ability to stimulate T cells
- no effect on IL-12, IL-10, IL-8 production
- no effect on IL-6 and TNF after TLR 2, 3, 4, 5, 6 stimulation
- decreased production of IL-6 and TNF after TLR 8 stimulation – reason of severe viral infection

Acknowledgement

Jiřina Bartůňková

Anna Šedivá

Jiří Litzman