

In patients with defects in Toll-like and Interleukin-1 receptor (TIR)-dependent signalling septic arthritis may present like Juvenile Idiopathic Arthritis

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Abbreviations:

JIA – Juvenile Idiopathic arthritis; TIR – Toll-like and Interleukin-1 Receptors; CrP – C-reactive protein; MyD88 – Myeloid differentiation Antigen 88; IRAK4 – Interleukin-1 Receptor Associated Kinase 4; NFκB – Nuclear Factor κB

To the editor: the International League of Associations for Rheumatology (ILAR) defines juvenile idiopathic arthritis (JIA) as arthritis of unknown origin beginning before the 16th birthday, persisting for at least 6 weeks; other known conditions are excluded [1]. Arthritis in JIA may show local warming, redness, swelling, pain or functional deficits but CrP-levels do usually not rise above 20 mg/l [2] whereas pyogenic arthritis mostly causes CrP-levels above 20 mg/l [3], although CrP-levels are not suitable to differentiate between septic and Lyme arthritis [4]. In contrast despite pyogenic arthritis patients with defects in

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12373

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TIR-MyD88-IRAK4-NF κ B-mediated signalling [5, 6] may present with low or delayed signs of inflammation [7].

The presented boy developed short swelling of the metacarpophalangeal joints at 2yrs. At 2yrs3mths temperature of 39°C, pain and effusion (MRI) in his right hip developed. *S.pneumoniae* (serotype 23B) grew in a blood culture; pyogenic arthritis was suspected and treated with cefuroxime intravenously. At 2yrs7mths - 8mths a bullous impetigo caused by *S.aureus* developed. At 2yrs9mths a coxitis of the left hip developed (treated with naproxen). At 3yrs of age he developed arthritis with effusion in the right hip and elbow and JIA was suspected (treated with naproxen). The patient was born at term; the umbilical cord fell 4 weeks after birth. His parents have a common great-grandmother.

Six weeks after manifestation of elbow arthritis he presented for the first time to our institution. His right elbow was strongly swollen, warm and bendable by only 60° but neither red nor painful (**Figure 1A**). On admission CrP was 11.6 mg/l (Normal < 5 mg/l), erythrocyte sedimentation rate 52 mm/h, hemoglobin 11.1 g/dl (11,7 – 14,7 g/dl), MCV 72 fl (77 – 96 fl), fibrinogen 4,66 g/l (1,6 – 4 g/l). Conventional x-ray and MRI revealed osteomyelitis (**Figure 1B - E**). Puncture of the joint revealed 37,3 polymorphnuclear cells/nl and Gram-positive diplococci, which also grew in a blood culture (*S.pneumoniae*, Serotype 23B). Due to the discrepancy between a septic arthritis on one side but only slight warming, no redness, no pain, only mildly elevated CrP, polymorphnuclear cells below 50/nl cells in the effusion on the other side, we suspected a primary immunodeficiency with impaired TIR-signalling. TIR-signalling controls the production of pro-inflammatory cytokines such as IL-6 and post-translational ectodomain shedding of L-selectin, CD62Ligand, CD62L (“CD62L shedding”) (see supplementary figure 1). A complete lack of IL-6 production and CD62L shedding of patient’s cells upon stimulation with Toll-like receptor agonists (**Figure 2**) and a homozygous mutation Q293X in *IRAK4* confirmed the hypothesis of a deficient TIR-signalling (see supplementary methods).

Before being diagnosed with autosomal-recessive IRAK4-deficiency the patient probably suffered three episodes of pyogenic arthritis and an extended skin infection. In retrospect JIA was unlikely as *S.pneumoniae* had been isolated in a previous blood culture at 2yrs3mths. In TIR-deficient signalling septic arthritis may be mistaken for JIA as both are not accompanied by strong acute phase responses. However patients with deficiencies in TIR-signalling may also develop strong acute phase responses if infections take a chronic course [8, 9]. So in pyogenic arthritis low inflammatory signs are highly suggestive for a defect in TIR-MyD88-IRAK4-NF κ B-mediated signalling but high inflammatory signs do not

exclude such defects. In conclusion, we propose to consider the search for primary immunodeficiencies in any infant or young child with septic arthritis.

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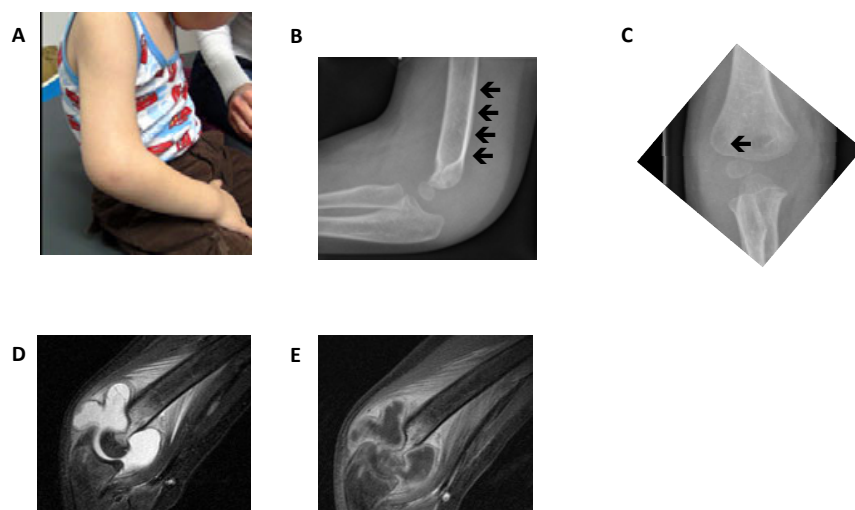


Figure 1

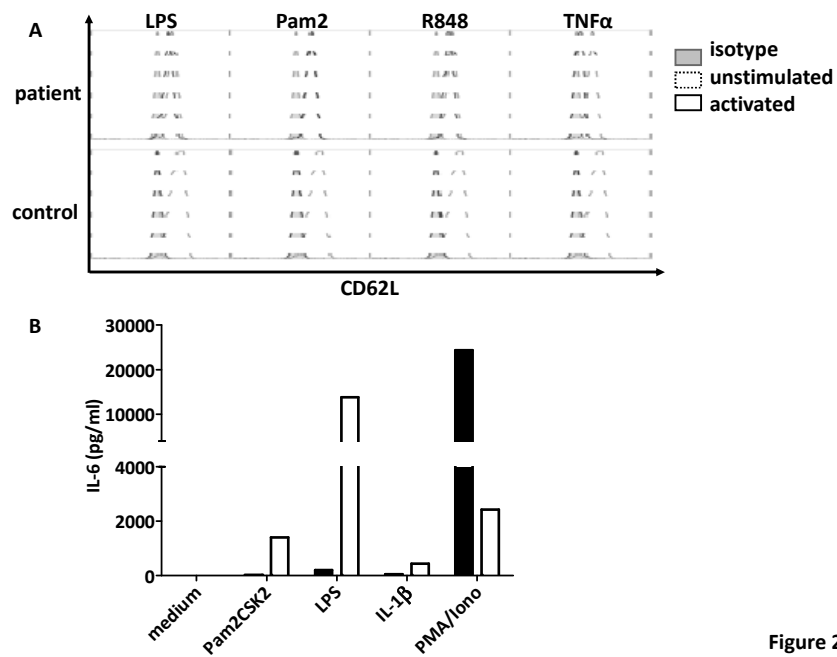
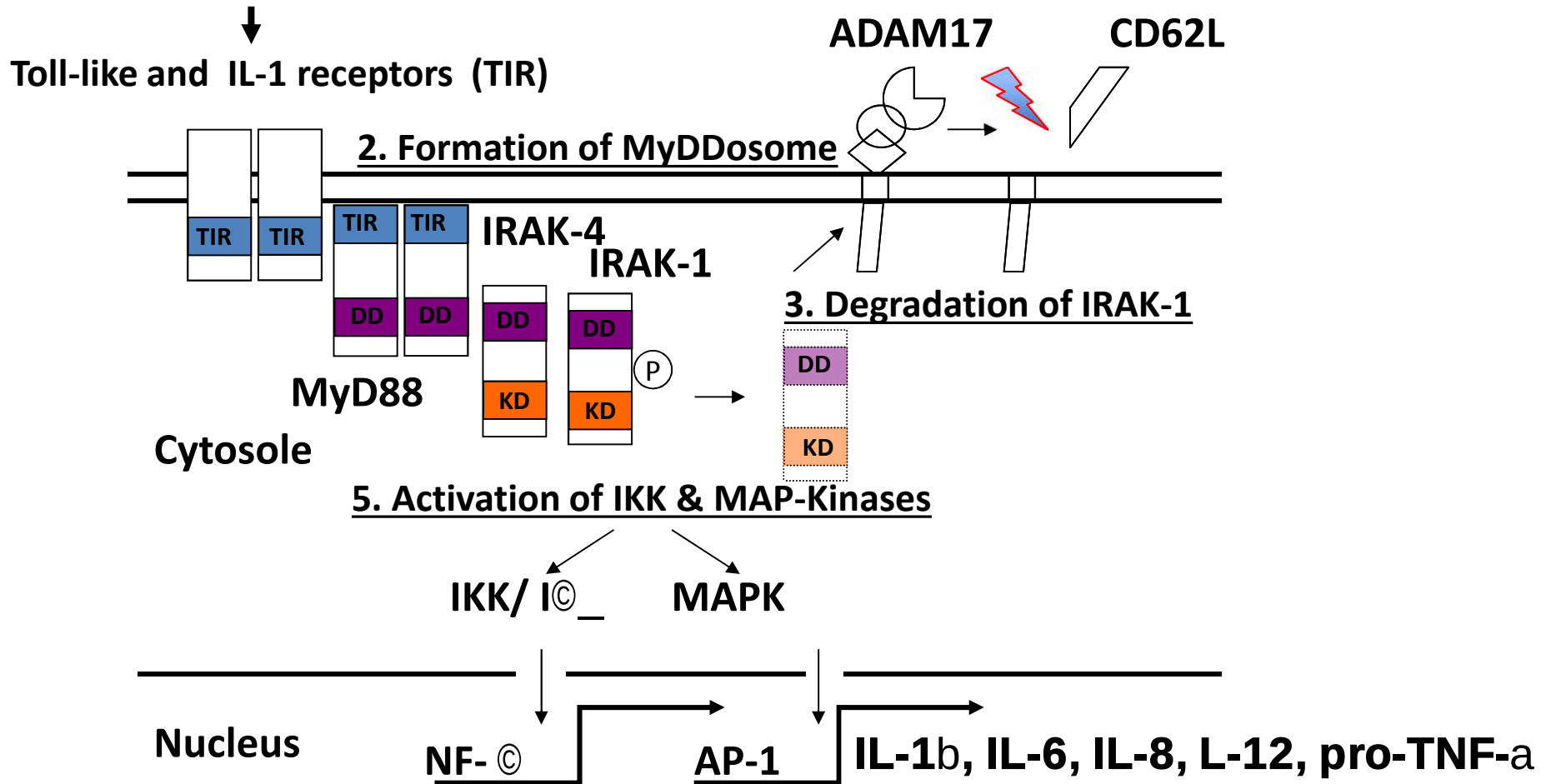


Figure 2

1. Activation of Toll-like and IL-1 receptors

Cytokines and TLR-agonists

4. Cleavage of CD62L by ADAM17 (« CD62L Shedding »)



Supplementary Methods

Surface CD62L expression on whole blood granulocytes was measured after stimulation with Pam₂CSK₄, lipopolysaccharide (LPS), phorbol myristate acetate (PMA) or tumor necrosis factor- α by flow cytometry. IL-6 and IL-10 concentrations in whole blood were determined after incubation with Pam₂CSK₄, LPS, recombinant human IL-1 β , TNF α and PMA/ionomycin for 48 hours by enzyme-linked immunosorbent assay [5, 6, 9].