Rheumatol Int (2012) 32:555–556
DOI 10.1007/s00296-010-1768-8

LETTER TO THE EDITOR

Pilot study: possible association of *IL10* promoter polymorphisms with CRMO

J. Hamel · D. Paul · M. Gahr · C. M. Hedrich

Received: 27 August 2010 / Accepted: 30 December 2010 / Published online: 15 January 2011

Dear Sir,

Chronic recurrent multifocal osteomyelitis (*CRMO*) is a form of non-bacterial osteitis. It has first been described in 1972 [1], and an association with pustolosis palmoplantaris [2, 3] and other autoimmune disorders, such as chronic inflammatory bowel disease (*IBD*), Wegener's disease, psoriasis, and Takayasu arteriitis has been discussed [3–7]. Little is known about the pathophysiology of *CRMO*. Several authors suggested slow-growing infectious pathogens [3], *Staphylococcus epidermidis* or *Propionibacterium acnes* [5, 8] as a potential cause. Since antibiotic agents do not influence disease progression and modern molecular techniques fail to detect infectious pathogens, these causes seem rather unlikely. Secondary to its association with other autoimmune diseases, various groups discussed an autoimmunological or pyogenic autoinflammatory cause of CRMO, and autoimmune inflammatory reactions as a response to infectious diseases [3, 9].

IL-10 is an immuno-regulatory cytokine that controls inflammation by limiting inflammatory cytokine expression. Dysregulation in IL-10 expression and single-nucleotide polymorphisms (*SNPs*) in the *IL10* promoter are associated with autoimmune and infectious diseases [10–14]. Most available studies were focused on a series of three *SNPs* in the 5′ proximal promoter. The *IL10* promoter polymorphisms $-1082G > A$ (rs1800896), $-819C > T$ (rs1800871), and $-592C > A$ (rs1800872) are in tight linkage disequilibrium and result in three predominant or "classical" haplotypes: ATA, ACC, and GCC. ATA and ACC have been shown to be associated with relatively low IL-10 expression, whereas GCC is associated with high IL-10 expression [10, 14]. Various studies demonstrated a correlation between *IL10* promoter *SNPs* and differential risk for infectious and autoimmune diseases [10].

Genomic DNA samples from 14 *CRMO* patients from the Pediatric Rheumatology and Immunology section, University Children's Hospital Dresden, Germany and 249 healthy controls were analyzed for three well-defined *IL10* promoter *SNPs* ($-1082G > A$, $-819C > T$, and $-592C > A$). We found an association of *IL10* promoter polymorphisms with *CRMO* and demonstrate an increased frequency of high IL-10 expressing $-1082G/G$ alleles (12/14 [0.86] vs. 27/249 [0.27]), and resulting GCC haplotypes (12/14 [0.86] vs. 56/249 [0.23]) (Fig. 1 a, b). GCC haplotypes are considered to be associated with high IL-10 expression. This is interesting, since IL-10 predominantly has immune-modulating functions. Secondary to its immuno-regulatory effects, dysregulation in IL-10 expression is associated with susceptibility to infectious and autoimmune diseases in humans and mice [10]. The association with GCC haplotypes might support the hypothesis that slow-growing pathogens, *Probionibacterium acnes, Staphylococcus epidermidis* or post-infectious autoimmune-autoinflammatory reactions might play a role in the pathophysiology of *CRMO*. Next to the anti-inflammatory aspects of IL-10 expression, IL-10 mediates the proliferation of various lymphocytic tissues, including B cells, and enhances antibody production [10]. Since predominantly lymphocytes, but also plasma cells can be found in biopsies, taken from *CRMO* lesions, an association with GCC haplotypes could partly explain the lymphocyte expansion in affected tissues [3]. Individual *IL10* promoter *SNPs* could also be part of extended haplotypes

J. Hamel · D. Paul · M. Gahr · C. M. Hedrich (✉)
Department of Pediatric Rheumatology and Immunology, University Children's Hospital Dresden, University Medical Center Carl Gustav Carus, University of Technology Dresden, Fetscherstr. 74, 01307 Dresden, Germany
e-mail: christian.hedrich@uniklinikum-dresden.de

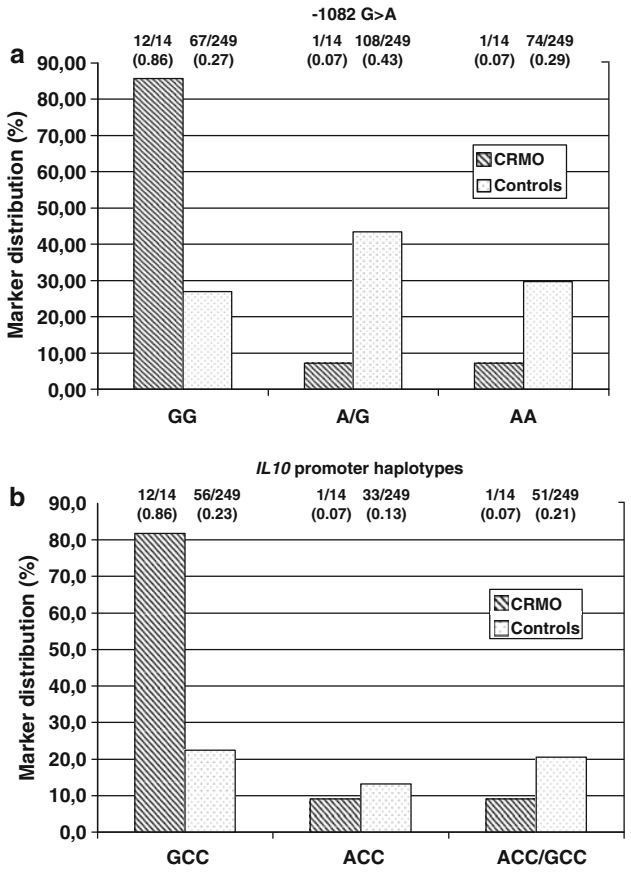

Fig. 1 *IL10* promoter polymorphisms in *CRMO*. **a** Results of a single-marker analysis of the *IL10* promoter polymorphisms −1082G > A are given. In *CRMO* patients, homozygous −1082G/G alleles are significantly more frequent, compared to healthy controls. **b** The paired allele frequency based on promoter haplotypes is given. In *CRMO* patients, homozygous GCC haplotypes are more frequent compared with normal controls

that may span several hundred kilobases over the entire *IL10* gene cluster [10, 12–15]. In agreement with this, a recent study failed to find a link between *IL10* promoter *SNPs* and *IBD*, but showed an association between a *SNP* 3′ to the *IL10* gene and ulcerative colitis [16].

To our knowledge, this is the first study that shows a possible association of *IL10* promoter polymorphisms with *CRMO*. Secondary to the low number of individuals, further studies are warranted in order to investigate an association of *IL10* promoter polymorphisms with *CRMO*. We would be pleased to collect samples from *CRMO* patients from Rheumatological centers, and to perform genotyping in order to get further insight into the association of *CRMO* with *IL10 SNPs* and extended *IL10* haplotypes.

References

1. Giedion A, Holthusen W, Masel LF, Vischer D (1972) Subacute and chronic "symmetrical" osteomyelitis. Ann Radiol (Paris) 15(3):329–342
2. Björkstén B, Gustavson KH, Eriksson B, Lindholm A, Nordström S (1978) Chronic recurrent multifocal osteomyelitis and pustulosis palmoplantaris. J Pediatr 93(2):227–231
3. Jurik AG (2004) Chronic recurrent multifocal osteomyelitis. Semin Musculoskelet Radiol 8(3):243–253
4. Huber AM, Lam PY, Duffy CM, Yeung RS, Ditchfield M, Laxer D, Cole WG, Kerr Graham H, Allen RC, Laxer RM (2002) Chronic recurrent multifocal osteomyelitis: clinical outcomes after more than five years of follow-up. J Pediatr 141(2):198–203
5. Schultz C, Holterhus PM, Seidel A, Jonas S, Barthel M, Kruse K, Bucsky P (1999) Chronic recurrent multifocal osteomyelitis in children. Pediatr Infect Dis J 18(11):1008–1013
6. Laxer RM, Shore AD, Manson D, King S, Silverman ED, Wilmot DM (1988) Chronic recurrent multifocal osteomyelitis and psoriasis—a report of a new association and review of related disorders. Semin Arthritis Rheum 17(4):260–270
7. Job-Deslandre C, Krebs S, Kahan A (2001) Chronic recurrent multifocal osteomyelitis: five-year outcomes in 14 pediatric cases. Joint Bone Spine 68(3):245–251
8. King SM, Laxer RM, Manson D, Gold R (1987) Chronic recurrent multifocal osteomyelitis: a noninfectious inflammatory process. Pediatr Infect Dis J 6(10):907–911
9. Kastner DL (2005) Hereditary periodic fever syndromes. Hematology Am Soc Hematol Educ Program 2005(1):74–81
10. Hedrich CM, Ramakrishnan A, Dabitao D, Wang F, Ranatunga D, Bream JH (2010) Dynamic DNA methylation patterns across the mouse and human IL10 genes during CD4+ T cell activation; influence of IL-27. Mol Immunol 48(1–3):73–81
11. Gibson AW, Edberg JC, Wu J et al (2001) Novel single nucleotide polymorphisms in the distal IL-10 promoter affect IL-10 production and enhance the risk of systemic lupus erythematosus. J Immunol 166(6):3915–3922
12. Mörmann M, Rieth H, Hua TD et al (2004) Mosaics of gene variations in the Interleukin-10 gene promoter affect interleukin-10 production depending on the stimulation used. Genes Immun 5(4):246–255
13. Salhi A, Rodrigues V Jr, Santoro F et al (2008) Immunological and genetic evidence for a crucial role of IL-10 in cutaneous lesions in humans infected with Leishmania braziliensis. J Immunol 180(9):6139–6148
14. Oleksyk TK, Shrestha S, Truelove AL et al (2009) Extended IL10 haplotypes and their association with HIV progression to AIDS. Genes Immun 10(4):309–322
15. Wilson JN, Rockett K, Keating B et al (2006) A hallmark of balancing selection is present at the promoter region of interleukin 10. Genes Immun 7(8):680–683
16. Franke A, Balschun T, Karlsen TH et al (2008) Sequence variants in IL10, ARPC2 and multiple other loci contribute to ulcerative colitis susceptibility. Nat Genet 40(11):1319–1323