are known to trigger cellular TLR2 signaling response and cytokine production that seems to inversely correlate to virulence.
Objective: We sought to investigate the role of SOCS-1 and -3 in pulmonary inflammation and in response to *mycobacteria* in vitro.
Methods: Human PBMCs, monocytes and alveolar macrophages (AM) were obtained through standard protocols from healthy individuals and patients with pulmonary disease due to non-tuberculous *mycobacteria* (NTM). Cells were stimulated in vitro with NTM (*M. avium*, ATCC 35717 and *M. abscessus*, ATCC 19977) for a period between 1-20 hours. Transcriptional response was assayed by real time PCR and protein detected by ELISA, Western blot and confocal microscopy evaluation.
Results: Kinetic experiments performed both on purified monocytes and AM showed induction of TNF-α after 20 hour culture by both *mycobacteria* and the early expression of SOCS-1 (8.6±1.3 fold induction compared to unstimulated cells) and SOCS-3 (6.2±2.0) induced by *M.avium* as compared to *M. abscessus*. Evaluation of such mediators on AM obtained from patients with pulmonary NTM infection confirmed mycobacteria-induced expression in the context of chronic disease (TNF-α, 4,940pg/ml; SOCS-1, 4 fold induction; SOCS-3, 4.3 fold). In order to determine whether knock down of SOCS-1 gene interfered with mycobacteria-induced response, we performed experiments using short-interfering RNA (siRNA) which led to higher expression (~50%) of TNF-α mRNA and protein in vitro.
Conclusion: The data suggest that *mycobacteria*-induced TNF-α production through TLR activation is partially regulated by SOCS. Moreover, our work indicates that different *mycobacteria* species elicit differential induction and activation of cellular effector mechanisms which may have correlates in virulence, pathogenesis, and clinical course of disease.

6
Mutation 1623_1624delGCinsTT and IL-12Rb1 Deficiency: A Mutational Founder Effect on the Most Frequently Affected Gene for Mendelian Susceptibility to Mycobacterial Disease

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Background: IL-12Rb1 deficiency is the most common genetic etiology of Mendelian susceptibility to Mycobacterial Disease (MSMD). Known mutations affecting the IL12Rb1 gene are recessive and associated to the abolition of the response to both IL-12 and IL-23. No studies on recurrent mutations have been reported so far. Mutation 1623_1624 delGCinsTT was described in 4 families (1 from Germany, 1 from Cyprus, 1 from France and 1 from Belgium). However, this same mutation was found in an unexpectedly high proportion among IL-12Rb1 deficient patients in Argentina: 6 (3 homozygous and 3 heterozygous) out of 7 affected individuals from 7 unrelated families carried this particular mutation.
Objective: To determine whether IL-12Rb1, 1623_1624delGCinsTT mutation represents a DNA mutational hotspot, or a founder effect where all mutants are identical by descent.
Materials and Methods: Thirty-four polymorphic markers in chromosome 19, internal or proximal to the IL-12Rb1 gene, were studied by direct sequencing, restriction fragment length polymorphism or microsatellite analysis in the Argentinian and the Belgium patients carrying mutation 1623_1624delGCinsTT, in order to determine if there was an haplotyte associated to this mutation. An in-house modified method for estimating the age of the most recent common ancestor carrying mutation 1623_1624delGCinsTT, and based on Génin et al. likelihood-based method, was applied. Two highly polymorphic markers were also studied in 100 normal chromosomes.
Results: A common haplotype was shared by all chromosomes carrying mutation 1623_1624delGCinsTT, whereas it was not detected on any of the control chromosomes. The age of mutation 1623_1624delGCinsTT was estimated in 22 generations (CI 95% 8-57) (1 generation % years).
Conclusions: Mutation 1623_1624 delGCinsTT represents a founder effect involving IL-12Rb1, the most frequently affected gene on patients with MSMD. Our calculations indicate this mutation arose 550 years ago (CI95% 200-1425), approximately by the time Spaniards' initiated colonization of the Americas. The reason(s) behind the persistency of this mutation across multiple generations, or if it confers any type of selective advantage has yet to be established.

7
Role of Innate Immunity in Viral Pathogenesis

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Background: The initial interactions between host and virus are critical in determining the ultimate outcome of the infection. These interactions include the ability of cells to engulf and eliminate viruses prior to spread. Cells encounter viral antigens: 1) On the surface (after initial attachment), 2) in endosomal compartments (after viral entry), and in the cytoplasm (after uncoating and exposure of the nucleic acid). Whether a virus causes hemorrhagic fever and shock (*Lymphocytic Choriomeningitis Virus* - LCMV and other *arenaviruses*) or encephalitis (*herpes simplex virus* - HSV) depends on the innate immune response to the virus.
Objective: To define the components of the innate immune responses to LCMV and HSV.
Methods: Human peripheral blood cells and mouse macrophages were challenged with live or uv inactivated LCMV or HSV. Levels of interferon and inflammatory cytokines were measured in cell supernatants as well as in the serum of wild type or TLR knockout mice.
Results: LCMV induced production of inflammatory cytokines is dependent upon the interaction of virus with Toll like receptor 2 (TLR2), a cell surface pattern recognition protein. The production of interferon by LCMV is regulated both by TLR2 (*in vivo*), as well as by cytoplasmic helicases (*in vivo*). The cytokine response to HSV (which determines whether there are symptoms of encephalitis) is