IL-27 receptor signaling is critical for B cell differentiation in collagen induced arthritis

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Disclosure

• Nothing to disclose

IL-27 is involved in initial Th1 cell commitment

Role of IL-27 in regulation of the immune cell functions

IL-27 and IL-27R expression

• IL-27 is expressed by antigen presenting cells (such as activated DCs and macrophages)

• IL-27R is expressed on naive T cells, NK cells, monocytes, mast cells, activated B cells and DCs

Our IL27R−/− mice lack the IL-27 specific WSX-1 subunit (IL-27Ralpha)
IL-27R−/− mice in EAE (mouse model for MS)

- Slightly higher incidence in IL27R−/− mice
- Significantly higher severity in IL27R−/− mice
- More IL-17A, IL-6, TNFα and IL17F production by draining lymph node cells
- More proliferation of lymph node cells


Proteoglycan (PG) induced arthritis

- Strongly Th1/IFN-γ mediated

Cao Y. et al, JI, 2008

IL-27 in collagen induced arthritis


Hypothesis

- IL-27 administration in CIA attenuates arthritis
- IL-27R−/− mice have more Th17 cells/fewer Th1 cells

More severe IL-17/Th17-mediated arthritis in IL-27R knock-out mice

Models:
- DTH
- (mBSA) AIA
- CIA

mBSA induced DTH

No difference in DTH in IL-27R−/− compared to wt mice
mBSA antigen-induced arthritis

mBSA antigen-induced arthritis: IL-17/Th17 mediated arthritis

T cell specific overexpression of GATA3 protects against development of severe joint inflammation

Critical role for IL-23 and IL-17 receptor signaling in the progression of non-autoimmune chronic inflammatory arthritis

J.P. Van Hamburg et al., Arthritis Rheum 2009, 60:750-9

Conclusion

Lack of IL-27 signaling has no effect on DTH and IL-17/Th17 mediated mBSA-induced arthritis

IL-23 and not IL-12 is required for the induction of disease

No increase of IL-17A expression in p19 deficient mice

Murphy et al., 2003

Lower incidence and severity of CIA in IL27R-/- mice
**FACS analysis of CD4+ T cells in spleen**

- **n=10 per group**

**FACS analysis of CD4+ T cells in spleen 10 days after immunization**

- **n=10 per group**

**FACS analysis of CD4+ T cells in joints 45 days after immunization**

- **n=10 per group**

**B cell development**

- Bone marrow
- Spleen & Lymph nodes

**FACS analysis of B cells 10/36/45 days after immunization**

**FACS analysis of B cells**

- IL27R-/- mice have lower-normal B cell numbers in CIA
- IL27R-/- mice have a lower % of follicular B cells at the peak of disease, which is normalized 45 days after immunization
- IL27R-/- mice have very few germinal center B cells at all timepoints after immunization

**Terminal B cell differentiation in T cell dependent immune responses is impaired?**
**Summary**

- Critical role of IL-27R signaling in the development of CIA:
  - IL-27R−/− mice: higher proportion of Th17 cells
  - IL-27R−/− mice: reduced numbers of CD4+ T cells and B cells early after immunization
  - IL-27R−/− mice: development of germinal center B cells was significantly impaired
  - IL-27R−/− mice: Collagen-specific IgG2a Ab levels were lower
  - IL-27R−/− mice: terminal B cell differentiation seems to be impaired

**Discussion**

- IL-27R signaling is involved in both T and B cell development and function
- Lack of germinal center B cell/plasma cells is most critical in IL-27R−/− mice for the reduced expression of CIA

**Acknowledgements**

Erasmus MC, University Medical Center
Rotterdam, The Netherlands

Department of Rheumatology

- Odilia Corneth
- Anne-Marie Mus
- Patrick Asmawidjaja
- Nadine Davelaar
- Maarten Brem
- Jan Piet van Hamburg
- Erik Lubberts

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