Summary

The studies presented here are an effort to use genetic models to study the interactions between the various cellular and molecular signaling interactions components involved in regulating an immune inflammatory response, and their eventual role in determining the balance between disease and health.

A. Role of signaling intermediate Btk in regulating cellular interactions in inflammation

1. Bruton's tyrosine kinase (BTK) in myeloid cells:

1.1 Role in eosinophil lineage

- Eosinophils constitute a high proportion of granulocytes in the XID/IL-5 Tg mice
- Compromised eosinophil recruitment and effector functions in XID/IL-5 Tg mice

Similar to its reported role in other myeloid cells, BTK seems to have a role in regulating eosinophil effector functions.

1.2 Role of the BTK-targeted transcription factor c-Rel in macrophage effector functions

- Peripheral blood circulating leukocytes frequencies in the c-Rel⁻/⁻ mice, remain unaltered
- Myeloid cell recruitment to sites of inflammation is unaltered in the c-Rel⁻/⁻ mice
- No compromise in myeloid cell effector functions in the c-Rel⁻/⁻ mice

Thus, indicating that c-Rel does not have a non-redundant role in mediating macrophage effector functions.

2. A role for BTK in T-B cell developmental cross-talk

- Severe reduction serum immunoglobulin levels in XID/nu and XID/TCRβ⁻/⁻ mice, with profound reduction in mature circulating B cells
Summary

- Early B cell developmental arrest at the pro/pre B cell stage in XID/TCRβ-/-
- B cell development is rescued with even a marginal increase in circulating T cells in the XID/nu, but peripheral maturation arrest seen in XID mice remains unaltered

XID mice, in the absence of circulating T cells, show severe agammaglobulinemia, profoundly reduced mature B cell frequency and an almost complete B cell developmental arrest, closely resembling XLA.

B. Role of lysosomal transporter LYST, in regulating myeloid cell functions

- Myeloid cells of bg/bg mice show no defect in recruitment to sites of inflammation
- bg/bg mice show increased susceptibility to cutaneous leishmaniasis
- bg/bg macrophages show compromised leishmanial clearance
- bg/bg mice show a Th1 biased T cells response on leishmanial infection
- IFN-γ primed bg/bg macrophages show enhanced leishmanial clearance

Thus, the enhanced susceptibility of bg/bg mice to cutaneous leishmaniasis does not result from an inability to mount an IFN-γ dominant-Th1 response, but is due to compromised parasite elimination by bg/bg macrophages.

C. The role of endogenous retroviral loci in controlling susceptibility to Lm infection

- CBA/J mice show chronic low-grade cutaneous leishmanial infection
- Chronicity of Lm infection is associated with inheritance of mtv-7
Summary

- Leishmania-specific T cell frequencies are equivalent in CBA/J and CBA/CaJ mice
- Leishmania-specific CBA/J T cells make lower levels of IFN-γ than CBA/CaJ T cells
- Low IFN-γ levels made by CBA/J T cells are not due to absence of v-SAg-7-reactive TCRβ subsets
- Leishmania-directed CBA/J and CBA/CaJ macrophage functions are similar
- APC identity in recall does not alter the level of IFN-γ production
- Altered T cell priming by CBA/J BMDCs is not immunogen independent

Thus, inheritance of the mtv-7 locus confers a disease specific increase in susceptibility to leishmaniasis, independent of its T cell deletion function and mediated by a quantitative rather than a qualitative modulation of the immune response.