ImmunoTools IT-Box-Cy55M-Award 2013

Clément Cocita

PhD Supervisor: Dr. Marc Dalod

Centre d'immunologie de Marseille Luminy,
Campus de Luminy
13009 Marseille, FRANCE

Role of MyD88 and Ly49H in promoting resistance to murine cytomegalovirus infection

The control of Murine Cytomegalovirus (MCMV) infection is known to rely on 2 mechanisms of innate immunity: i) virus recognition by dendritic cells (DC) through their endosomal Toll Like Receptors (TLR) 7 and 9, leading to the synthesis of antiviral cytokines via a signaling cascade dependent on the adaptor molecules MyD88 and IRAK4, and ii) recognition and killing of infected cells by Natural Killer (NK) cells expressing adequate activation receptors such as Ly49H or Ly49P. However, the relative importance of these 2 mechanisms in the control of infection is unclear. To understand this issue, we examined resistance to MCMV infection in 4 BALB/c congenic mouse strains deficient for Ly49H, MyD88 or both. 3 days post-infection (pi), only $Ly49H^+$ mice controlled viral replication in the spleen and liver. However, at day 6 pi, both $Ly49H^-MyD88^+$ and $Ly49H^+MyD88^-$ mice, but not double deficient $Ly49H^-MyD88^-$ animals, had also achieved MCMV control. Antibody-mediated NK cell depletion *in vivo* impaired late viral control in $Ly49H^+MyD88^-$ mice but not in $Ly49H^+MyD88^+$ mice. At moderate doses of viral inoculum, only $Ly49H^-MyD88^-$ mice succumbed to MCMV infection. Hence, both MyD88 and Ly49H were required for control of MCMV early after infection. However, upon moderate dose infection, MyD88 and Ly49H were redundant for late control of MCMV replication and for the promotion of health over disease. MyD88 was instrumental for efficient activation of DC and NK cells in $Ly49H^-$ but not in $Ly49H^+$ mice. Double deficient $Ly49H^-MyD88^-$ mice failed to mount strong MCMV-specific CD8 T cell responses, which was associated with a major attrition of splenocytes and with extensive tissue damage in spleen and liver as compared to the 3 other mouse strains studied. Thus, our results demonstrate that MyD88 is dispensable for the induction of efficient innate and adaptive immune responses against moderate dose MCMV infection in animals which NK cells are able to directly recognize and kill infected cells through the engagement of an activation receptor. This might explain in part why MyD88 and IRAK4 have been reported to be redundant for immunity against viruses in humans. This observation could thus help reconciling the conclusions drawn on antiviral immune defenses from the analysis of animal models as compared to the study of human immunity *in natura*.

With the recombinant proteins from the IT-Box CY55M, we would like to induce the bone marrow-derived dendritic cell (BMDC) differentiation from the 4 mouse strains, and co-culture these BMDC with NK cells from the 4 mouse strains upon MCMV stimulation, in order to understand the mechanisms involved in the NK cell activation by DC during viral infection.

ImmunoTools IT-Box-Cy55M for Clément Cocita

includes 55 recombinant mouse cytokines

rm EGF, rm Eotaxin / CCL11, rm FGF-a / FGF-1, rm FGF-b / FGF-2, rm FGF-8, rm Flt3L / CD135, rm G-CSF, rm GM-CSF, rm GRO-a / CXCL1, rm GRO-b / CXCL2, rm IFNgamma, rm IL-1alpha, rm IL-1beta, rm IL-2, rmIL-3, rm IL-4, rm IL-5, rm IL-6, rm IL-7, rm IL-9, rm IL-10, rm IL-11, rm IL-13, rm IL-15, rm IL-16, rm IL-17A, rm IL-17C, rm IL-17F, rm IL-19, rm IL-20, rm IL-21, rm IL-22, rm IL-25 / IL-17E, rm IL-27, rm IL-31, rm IL-33, rm IP-10 / CXCL10, rm LIF, rm MCP1 / CCL2, rm M-CSF, rm MIP-1α/ CCL3, rm MIP-1β / CCL4, rm MIP3α / CCL20, rm MIP3β / CCL19, rm NGF-beta, rm PDGF-AA, rm PDGF-BB, rm RANTES / CCL5, rm sCD40L / CD154, rm SCF, rm SDF-1α / CXCL12a, rm SDF-1β / CXCL12b, rm TNFα, rm TPO, rm VEGF DETAILS