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Fabrice Laurent

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## How innate immune responses shape *Cryptosporidium* infection

F. Laurent

UMR1282 Infectiologie et Santé Publique, INRA Centre Val de Loire, Université François Rabelais de Tours, 37380 Nouzilly, France

Immune status of the host is of critical importance for controlling *Cryptosporidium* infection. Logically cryptosporidiosis primarily affects young ruminants, infants, and immunocompromised individuals. The infection is transient in immunocompetent individuals but severe in young mammals in particular when exacerbated by malnutrition and persistent in adults with immune deficiency. Cryptosporidiosis is still poorly controlled by chemotherapy and available FDA approved molecule Nitazoxanide (NTZ) require for its efficacy the presence of a certain level of host immunity. Indeed, oral suspension and Nitazoxanide tablets have not been shown to be superior to placebo for the treatment of diarrhea caused by *Cryptosporidium* in HIV-infected or immunodeficient patients. Therefore, understanding immune mechanisms controlling parasite replication and host pathology is a prerequisite for developing host-directed therapies for controlling cryptosporidiosis alone or in combination with chemotherapy.

*Cryptosporidium* is minimally invasive and its development is restricted to the apical side of epithelial cells *in vivo*. Intestinal epithelial cells (IECs) are therefore central in the mechanisms of protection representing the watchdog of the immune system, signaling the infection to the immune system by releasing soluble mediators such as chemokines but also *Cryptosporidium* antigens via small vesicles, and apoptotic bodies. Murine models allowing deep investigation of immune mechanism demonstrate that induction of an adaptive immune response is required for a definitive clearance of the infection but innate immunity plays the main role in controlling the acute phase of the disease. Proportions of the subsets evolve in young animals the days following birth and are also deeply modified by the infection. Among the four conventional dendritic cell (cDC) subsets present in the neonatal intestine we identified CD103+ Batf3+ DC (cDC1) as the key subset by their ability to produce large amount of IL12 which in turn can activate T lymphocytes, NK cells and ILC1 to produce IFN $\gamma$  a cytokine known to restrict *C. parvum* growth in intestinal epithelial cells. We are currently characterizing the cDC1 cells in lymphoid and non-lymphoid intestinal tissues in ruminants to validate our findings in a target species. A strong recruitment of immune cells in close contact to infected IEC is not necessarily linked to protection. We have indeed observed that the large influx of Ly6-C inflammatory monocytes during infection has no effect on parasite replication rate but was linked to intestinal permeability with a possible link with physiopathology. This highlight the importance of being able to transform observations and correlations into functional demonstrations. When immunomodulatory treatments affecting mononuclear phagocytes are investigated, it is therefore important to identify their role on both cDC1 and inflammatory monocytes and to evaluate the general benefit for the host. Once effectors cells are activated, they in turn produce immune mediators acting on IEC. Another way to strengthen the efficacy of immune responses is to identify evasion strategies implemented by the parasite. Several mechanisms have been identified to date including parasite immune evasion through miRNA-mediated mechanisms induced in IECs. During infection alterations in miRNA expression profiles affect epithelial cell immune and inflammatory response and release of apical and basolateral exosomal vesicles.

We need to continue our efforts on preventive and control measures to fight the disease. The combination of host immune modulation with new chemotherapeutic solutions currently in active development in many laboratories represents a very attractive way for efficiently control the disease.