The intestinal mucosa is exposed to an enormous antigenic load of alimentary and microbial origin. To protect its surface from potentially harmful aggressions while guaranteeing tolerance towards harmless antigens (i.e. of alimentary origin or the commensal microbiota), this intestinal mucosa evolved several strategies, resulting in an efficacious epithelial barrier and a highly organized mucosal immune system. There is good experimental evidence that the intestinal microbiota is a main driver of the development of the mucosal immune system, with a critical phase during initial colonization after birth [1, 2]. Therefore, it is easily understandable that perturbations/changes of the colonization process may cause health problems with short- and eventually long-term consequences. Examples of diseases resulting from a disturbed microbial-host interaction are numerous, such as allergic diseases or dysimmune disorders, particularly those involving the intestinal tract, such as inflammatory bowel diseases [3, 4]. Research over the last years allowed gaining profound insight into the regulation of the immune system, the dialogue with the microbial environment, as well as the potential impact of food-derived antigens on pathological inflammation. These advances were largely stimulated by the introduction of new experimental disease models, such as experimental colitis models, as well as by the discovery of distinct human diseases, highlighting defects in key steps of immune regulation. However, many open questions remain, i.e. the initial triggers causing chronic intestinal inflammation, such as inflammatory bowel disease, the cause of food intolerance or the reason for loss of tolerance or inability to acquire tolerance. Given the important task to protect the intestinal mucosa, while enabling the uptake of large amounts of nutritional products, it is not surprising that the intestine harbors over 70% of immune-competent cells and produces a high amount of immunoglobulins. For the recognition of antigenic
or foreign structures (of alimentary of microbial origin), macrophages and dendritic cells (DC) play an extremely important role. These antigen-presenting cells sense microbial and other antigenic structures in the intestinal lumen and initiate immune responses. It is surprising to note that an immune response elicited by intestinal DC differs markedly from those initiated by spleen-derived DC: intestinal DC induce anti-inflammatory and tolerogenic responses to harmless antigens such as those derived from the resident microflora or harmless food allergens, while systemic immune activation results in a strong inflammatory TH1/TH17 reaction. Recent research has clearly confirmed that the functions of DC are regulated and imprinted by the microenvironment [5]: high concentrations of retinoic acid or vitamin D metabolites, as well as thymic stromal lymphopoietin and transforming growth factor (TGF)-β activate signaling programs in DC that result in the priming of regulatory and anti-inflammatory T cell responses (fig. 1). This interaction between DC and the microenvironment is highly dynamic, and the process is called DC priming or conditioning. TGF-β is one of the key factors implicated in intestinal immune regulation; it is produced by a large variety of cells in the intestinal mucosa, including intestinal epithelial cells, lymphocytes and monocytes/macrophages/DC. Three distinct isoforms of TGF-β exist exhibiting similar pleiotropic properties.

Fig. 1. DC conditioning. Effect of the environment on DC function and subsequent T cell priming.
An important anti-inflammatory effect of TGF-β on the immune system is the promotion and generation of FOXP3-positive regulatory T cells in the intestinal compartment. There are first and encouraging data from studies in Crohn’s disease, an inflammatory GI condition, that used enteral therapy with optimized concentrations of immunoregulatory peptides, such as TGF-β.

References