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Immunoregulation: A Proposal for an Experimental Model

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1. Introduction

The scope of the chapter is to describe principles and mechanisms of activation and regulation of porcine intestinal immune system, especially during postnatal development. The pig is an essential source of food Worldwide, and thus, immunological research in swine husbandry and nutrition is performed to develop a safe and sustainable meat production. The study of the swine mucosal immune system is important because induction and maintenance of protective immune mechanisms will be at the cost of energy which will be lost for productive purpose. Also, certain degree of mucosal immune response is necessary to protect against chronic and acute infectious diseases that can cause losses in production, but on the other side, overacting immune responses can be detrimental for the host. Further, the pig is important biomedical model for applied experimental studies in different areas of physiology or clinical medicine. In particular, the pig is important for transplantation research, both for the development of surgical techniques and as xenotransplant donor. Thus, it is of importance to understand porcine immunology and to obtain insight into the structure and functional characteristics of their humoral and cellular immune system, both systemic and local. Herein, we propose the pig as a model for immunoregulation at the mucosal surfaces of the gut. The gut and gut associated lymphoid tissue (GALT) has dual roles in mammals organism: digestion and apsorption of nutrients as well as protecting the body from harmful pathogens and inducing tolerogenic responses to self-antigens, food particles and commensals. The unique architecture of the GI tract facilitates both of these functions.The purpose of this chapter is to review the existing literature on developmental aspects of antigen handling and processing by intestinal mucosal immune system of developing pigs.

The immune defence system of the gut consists of lymphoid tissues and cells distributed along the gastrointestinal tract. Important features that characterize the mucosal immune system are:

- Mucosa-associated lymphoid tissue (MALT or GALT-gut associated lymphoid tissue) with local and regional lymph nodes (LNs) where the induction of immune responses is established (Payer's patches and the mesenterial lymph nodes)
- Certain subpopulation of lymphoid cells at the mucosal surfaces
- Mucosal homing, that means specific recirculation of mucosal lymphocytes towards mucosae
- Predominant mucosal immunoglobulin is IgA secreted at the mucosal surface.

2. Intestinal mucosal immune system (IMIS): Paradoxycal role to protect and/or tolerate

The concept of mucosal immunity includes response to harmful antigens and also control of harmless antigens to prevent inflammation, well known as mucosal or oral tolerance. Therefore the mucosal immune system has to retain the ability to respond actively to pathogens, while avoiding active potentially inflammatory responses to pathogens. For that reason, the organisms have decision-making pathways embedded with the immunological architecture of the mucosal immune system. If a little dietary antigen access to the general circulation a systemic immune response may be prevented by the activities of regulatory T cells. Oral tolerance develops to the antigen. It involves either cellular suppression or clonal anergy and it is directed against Th1 cells (Gad, 2005). Which mechanism would be involved depends on several things. The feeding of novel protein antigens is associated with the presence of mucosal IgA responses despite the appearance of systemic oral tolerance. There is a strong genetic influence on the extent of systemic tolerance induced by feeding. Dose of orally administered antigen is important. Low doses invoke priming; high doses provoke clonal anergy (oral tolerance). Several studies, including humans, swine and mice, demonstrated that small quantities of food proteins absorb intact across the intestinal epithelium in adults and neonates (Bailey et al, 1994; Telemo et al, 1991). Recent studies of the phenomenon of oral tolerance suggest that it is variable and age-dependent (Bailey & Haverson, 2006) as well as the present of commensal microbial flora in the intestine.

2.1 Structure of the intestinal mucosal immune system (IMIS)

The mucosal immune system is described as the subset of immunological components, which appear in or associated with mucosal tissues. In mammals, there is clear distinction between primary lymphoid tissue, such as the bone marrow and the thymus, and secondary lymphoid tissue such as the spleen and organised lymph nodes and Payer's patches. Since mucosal tissues are exposed to the harmless and harmful antigens, mechanisms must activate appropriate, but different responses to different types of antigens. Therefore we use classic differentiation mucosal immune system on the organised and the diffuse lymphoid tissues.

The organised lymphoid tissues include the Payer's patches and the mesenteric lymph nodes. There's role is recognition of luminally presented antigens through different pathways:

1. Some antigens cross the epithelium membrane of the villi owing the dendritic lineage which are underneath the intestinal epithelium. Dendritic cells with dendrites uptake antigen through the epithelium by manipulation tight-cell junction (Rescigno et al., 2001, MacPherson & Uhr, 2004). Dendritic cells may also phagocytose epithelial cells together with environmental antigens (Huang et al., 2000) or ensure crossing the epithelium intact, transcellularly or paracellularly (Jang et al., 2004). Mucosal dendritic cells migrate through afferent lymphatics to the mesenteric lymph nodes, where they can present antigen in T-cell areas. So, the mesenteric lymph nodes are important for initiation or expansion of mucosal immune responses (Mowat, 2003).
2. Antigen may be taken up directly to the Payer's patches mediated by specialised M-cells or paracellularly by dendritic cells. Migration of this cells to the T-cell zones results in T-cell activation, migration and induction of responses in the follicle of the Payer's patch. Primed T- and B-cells emigrate from the patches in efferent lymphatics (Brandtzaeg & Pabst, 2004).

3. Intact antigen absorbed across the mucosal epithelium may reach the lymphatics directly and be transported to the lymph nodes and into blood, where it can interact with components of the systemic immune system (Telemo el al., 1991).
4. Antigens may cross the enterocytes epithelial membrane in the form of exosomes. Pig enterocytes do not express MHC II proteins on their surfaces, but capillary lymphoid tissue epithelium in the pig's intestine expresses high levels of MHC II molecules, so it could be possible that these cells release exosomes directly into blood (Wilson et al., 1996).

The diffuse lymphoid tissues

Different cells and molecules are present into mucus membrane of the pigs' gastrointestinal tract.

1. Intestinal epithelium contains some amount of leucocytes. The predominant lymphocyte population express the CD8 coreceptors, unconventional subset of T-cells expressing a CD8αα homodimer and the TCR chains (Hayday et al., 2001). The majority of lymphocytes in the intestinal epithelium express CD2. A high proportion of lymphocytes express $CD8^+$ in adults which do not appear in piglets until 7 weeks onwards (Whary et al., 1995). In young pigs, intestinal epithelium lymphocytes are mostly $CD2^-CD4^-CD8^-$, and during the first few weeks of life $CD2^+CD4^-CD8^-$ appear.
2. Lamina propria underneath the epithelium is well supplied with leukocytes and in pigs shows a high level of organisation (Wilson et al., 1996). Theirs' APCs expressing MHC II protein class. Immature dendritic cells are present in large numbers within the villi and co-localise with T-cells expressing the CD4 coreceptor in the pig, but expressing the low affinity FcγRIII (Bailey & Haverson, 2006). The point is that diffuse mucosal tissue has the first role in immune regulation, rather than active defensive responses. At the same time, these plastic cells may easiliy be switched from regulatory to active responses (Mellman & Steinman, 2001).
3. The endothelium of the capillary plexus beneath the epithelial basement membrane expresses MHC II molecules as good as dendritic cells. There are also dendritic cells within the villi and help to promote CD4 co-receptor with T-cells.
4. Lamina propria around intestinal crypts consists of cells staning for immunoglobulin (IgA, presumably plasma cells) and myeloid lineage cells have more characteristic of macrophages and granulocytes (Vega-Lopez et al., 1993). Plasma cells are predominantly IgA^+, IgM^+ and some IgG^+cells are present.

2.2 The role of antigen presenting dendritic cells

The role of population of dendritic cells (DCs) in the intestine and associated lymphoid tissues is of great interest because theirs influence in maintenance of tolerance towards the commensal microflora and in protection against pathogens. There are unique functional properties of populations of intestinal DC, as well as the type of signals that are necessary for them to mediate these functions. The intestine and GALT have network of cells with antigen-presenting function, including macrophages, DCs (CD11c) and plasmacytoid DCs (Smith et al., 2005; Iwasaki A, 2007). Various subpopulations of DCs are present in the organized lymphoid tissue of the intestine, Payer's patches and mesenteric lymph nodes, through the small intestine and lamina propria (Johansson & Kelsall, 2005). Dendritic cells have a central role in the activation of resting T cells and the initiation of primary responses. DCs acquire antigen (Ag) in peripheral tissues and transport it to lymph nodes (LNs) for

presentation to lymphocytes (Banchereau & Steinman, 1998). DCs migrate constitutively from peripheral tissue when they have acquired foreign Ag, but also in the absence of any antigenic or inflammatory stimuli (Huang et al., 2000). However, DCs continually migrate from the intestine to mesenteric LNs in the absence of overt antigenic stimulation (Liu et al., 1998). Plasmacytoid dendritic cells (pDC) recognize pathogen molecules, particularly viral, and play crucial roles in the inate defense and regulation of adaptive immune responses (Colonna et al., 2004). pDCs function primarily via TLRs and ligation of these receptors stimulates the secretion of large amounts of cytokines, particularly IFN (Asselin-Paturel & Trinchieri, 2005).

Theirs functional properties vary according to their anatomical location. Activated DC from the Payer's patches produce higher levels of interleukin 10 (IL-10), than splenic DC (Iwasaki & Kelsall, 1999). Naive CD4 T-cells activated by DC from the Payer's patches produce higher levels of IL-4 and IL-10, indicative of a T helper (T_H2) type phenotype, than those activated by splenic DC. Surface phenotypic analysis of CD11c1 DC populations revealed that Payer's patches DCs expressed higher levels of major histocompatibility complex class II molecules, but similar levels of costimulatory molecules and adhesion molecules compared with splenic DCs. But, the level of IFN-g produced by T cells primed with spleen DCs was significantly higher than that produced by T cells primed with PP DCs. While presentation of antigen by DCs *in vitro* leads to T cell activation, the same may not apply *in vivo*, and there is circumstantial evidence that DCs may be able to present Ag in a tolerogenic manner (Finkelman et al., 1996, Viney et al., 1998).

Activated pDCs secrete proinflammatory cytokines, change their morphology from a round cell to dendritic cell-like, up-regulate MHC and costimulatory molecules and become effective APCs. Human pDCs activated by CD40L or influenza virus can induce proliferation and polarization of T cells. Mature pDCs efficiently stimulate T cells and drive a potent TH1 polarization in vitro, which is mediated by the synergistic effect of interleukin 12 and type I interferon. In vivo, mature pDCs are found in secondary lymphoid organs, where they represent the principal source of type I interferon during inflammation (Cella et al., 2000). Mice pDCs activated with virus have shown to activate naive CD8+ T cells and to promote and polarization of Ag-experienced unpolarized CD4+ T cells (Krug et al., 2003). pDCs have a role in tolerogenic responses, as they can induce development of anergic T cells or T cells with regulatory function in vitro (Moseman et al., 2004). It is known now that depletion of pDCs can lead to airway hyperactivity to normally inert inhaled Ags, and that adoptive transfer of Ag-loaded pDCs before sensitization could prevent the induced asthma (De Heer et al., 2004). In this case Ag bearing pDCs was isolated from lung and the draining LN which suggested that similarly to classical DC, pDCs may acquire Ag at mucosal sites and transport it to the induce tolerogenic responses. There was no evidence for migration pDC in afferent lymph under steady state condition. However, Yrlid et al., (2006) showed that pDCs are not present in afferent lymph draining another mucosal tissue, especially the intestine. It is possible that the absence of pDCs in intestinal lymph is only in steady-state condition. These experiments suggest that pDCs present in mucosal tissues and liver do not induce tolerogenic or immunogenic Ag-specific T cell responses by acquiring Ag in the periphery and transporting it via afferent lymph to the draining lymph node. The mechanisms of acquiring Ag from periphery is unknown, potential mechanisms include delivery by classical DCs or exosomes or release of DC fragments (Villadangos & Heath, 2005).

Dendritic cells in human are classified according to their cell-surface receptor expression into several subsets. In the Payer's patches, conventional DCs are $CD11c^{hi}CD11b^{+}CD8\alpha^{-}$, $CD11c^{hi}CD11b^{-}CD8\alpha^{-}$ and $CD11c^{hi}CD11b^{-}CD8\alpha^{+}$ subtypes, with unique anatomical localisation and functional properties. These DC can also be described in terms of their expression of the chemokine receptors CX_3C chemokine receptor 1 (CX_3CR1) and CC chemokine receptor 6 (CCR6, Salazar-Gonzalez et al., 2006). CX_3CR1^{+} DCs were found to be associated with the follicle-associated epithelium in the steady state, whereas $CCR6^{+}$ was recruited from the subepithelial dome to the follicle-associated epithelium during infection (Salazar-Gonzalez et al., 2006). An additional population of CD11cmid plasmacytoid DCs are present in the Payer's patches and MLN, but they do not migrate from the intestine to the MLN (Yrlid et al., 2006). Similar subset composition we can find in the small intestinal lamina propria DCs. DCs in the small-intestinal lamina propria were found to express CX_3CR1 (Niess et al., 2005). In the colon, DCs appear to be concentrated within isolated lymphoid follicles, with very few present in the lamina propria under steady-state conditions. MLNs contain population of DCs written before, but they are both migratory DCs arriving from the intestinal lamina propria in the steady-state and resident DCs that have developed from blood-home precursors. Functional differences depend on developmental origins, local environmental conditions and maturation states (Coombes & Powrie, 2008). $CD11b^{+}$ DCs can be found in the subepithelial dome of the Payer's patches, whereas $CD8\alpha^{+}$ is present in the inter-follicular region. While $0CD11b^{+}$ DCs from the Payer's patches produce IL-10 and prime Th2 cells, $CD8\alpha^{+}$ and $CD11b^{-}CD8\alpha^{-}$ were shown to produce IL-12 and interferon-γ (IFN-γ) by T-cells. Jejunal lamina propria in pigs contains large number of MHC class II cells, which could be divided into at least three subsets based upon expression of other markers. The majority of MHC class II co-expressed on $CD45^{+}$ cells, and second population of cells expressing CD16, SwC3 and CD45. Actually, there are $CD45^{+}$ and $CD45^{-}$ cells which very differ morphologically. The $CD45^{+}$ cells are large, strongly adherent and had bilobed nuclei. The CD^{-} is smaller and elongated with dense oval nuclei (Stokes & Bailey, 2000). Haverson & Riffault (2006) found that $CD45^{+}$ population was potent stimulators of primary responses, but $CD45^{-}$ stromal population were unable to generate any proliferative response. Further, there are identified some unusual APC DC such as expressing both CD11c and MHC II at low intensity. These DC produced immune-regulatory cytokines such as IL-10 and type I IFN, suggesting a role in immunoregulation and tolerance induction. These intestinal DCs are capable of presenting antigen and induce tolerance, but also can response to inflammatory stimuli to allow T cell priming and protective immunity (Mowat, 2005).

DCs are separate lineage that is present in the steady state, but they have ability to run pro-inflammatory responses. Alternatively, these cells may represent population of DCs in steady state but becomes more dominant during inflammation (Coombes & Powrie, 2008). Intestinal macrophages display some characteristics compared with splenic macrophages or those that derive from blood monocytes (Smythies et al., 2005). Human intestinal macrophages retain phagocytic and bactericidal activity, but they lack CD14 expression, which is obligatory for the Toll-like receptor 4 (TLR4)-mediated recognition of ligands. These cells showed an impaired ability to produce proinflammatory cytokines. These modifications might contribute to intestinal immune homeostasis by ensuring the contact of intestinal APCs with microbial products do not result in the generation of potentially destructive inflammatory responses.

2.3 Intraepithelial and lamina propria lymphocytes (IEL, LPL)

Different antigens enter the body from the intestine: food proteins, commensal gut flora, invading pathogens, toxins. The digestive tube is lined by a continuous monolayer of epithelial cells. That intestinal epithelial cells (IEC) act as a physical barrier, separating the contents of a luminal environment from the layers of tissue comprising the interior milieu (Gewirtz et al., 2002). IEC also participate in the innate immune response of the intestine like a physical barrier, mucus secretion, antibacterial peptide synthesis and participation in the cytokine/chemokine network (Oswald, 2006).

2.3.1 Intraepithelial Lymphocytes (IEL)

At the basolateral surfaces of intestinal epithelial cells there are intestinal intraepithelial lymphocytes (IEL) which play important roles in the homeostasis of intestinal microenvironment. Intraepithelial lymphocytes (IEL) are predominantly T lymphocytes, a major subpopulation of γδ i-IEL is produced from uncommitted precursors at extrathymic sites (Bandeira et al., 1991; Poussier & Julius, 1994). T cells appear to have both proinflammatory and regulatory functions: they can act as a bridge between innate and adaptive immunity early in responses and can down-modulate inflammatory responses (Newton et al., 2006).

In samples of proximal and distal small intestine of five 6-month-old pigs (Vega-Lopez et al., 1995) were studied CD2, CD4 (helper/inducer T-cells), CD8 (suppressor/cytotoxic T cells), accessory cell marker (monocyte/granulocyte) and MHC Class II (DRw) receptor. $CD2^+$ cells were found in high numbers in both the epithelium and the lamina propria. Two subpopulations of intraepithelial lymphocytes were identified: apically in the epithelium there were $CD2^+CD4^-CD8^-$(double negative) cells, whereas cells expressing CD8 marker were concentrated around the basement membrane. $CD4^+$cells were localized in the lamina propria towards the villus core. Accessory cells were distributed in crypts and the villus base and more cells were found in ileum than in duodenum. In contrast, MHC Class II^+ cells were located predominantly in villi, just underneath the basement membrane, forming a sheath of cells between the $CD8^+$ and the $CD4^+$ cells. Pig IEL express CD2 and have an increased proportion of CD8+ cells (Stokes et al., 2001; Davis et al., 2004). However, neonatal pigs are mostly $CD2^-CD4^-CD8^-$, and $CD8^+$ IEL cannot be recognized until the animal matures. Bailey et al. (2001) confirmed the infiltration of $CD8^+$ T cells within the intestinal lamina propria of the villi from 4 week of age onward. It has also been demonstrated that phenotypic changes in porcine IEL are influenced by exposure to environmental antigens (Pabst & Rothkotter, 1999, Bailey et al., 2005). McCracken et al. (1999) reported that the number of $CD8^+$ T lymphocytes per 100 m of villus isolated from the intestinal jejunum was increased post weaning.

According to morphology, size, and sedimentation density of lymphocytes, Hayday et al., (2001) have proposed that IEL be classified into 2 subgroups: Type a and Type b. As Type a IEL would be included intraepithelial lymphocytes that are thymus-dependent, activated within the peripheral circulation, that express the αβ T-cell receptor, and that recognize antigen in the context of major histocompatibility complex I or II. Type b IEL are thymus-independent cells that express T-cell receptors that are $γδ^+$, $γδ^+CD8αα^+$, or $αβ^+CD8αα^+$. Both types of IEL are cytolytic effectors that secrete cytokine and chemokine mediators. Havran et al. (2005) supported the idea that intraepithelial $γδ^+$ T cells are involved in tissue repair, lysis of damaged epithelial cells, and inflammatory cell recruitment (qualified like innate immune response), while type a IEL are more indicative of an adaptive response. Egan et al

(2011) showed that αβ and not γδ T-cell IELs mediate intestinal damage in mice after parasite infection. In that case IELs did not function alone to cause inflammatory lesions, but acted with $CD4^+$ T lymphocytes from the lamina propria (LP). IEL has ability to bind to E cadherin on IEC, which is facilitated by the expression of αEβ7 integrin (Cepek et al., 1994). Zuckermann and Gaskins (1996) reported that mucosa-associated lymphoid tissues had significantly smaller proportions of $CD4^+$ and/or $CD8^+$ T cells than lymph nodes and CD4/CD8 double positive cells accounted for a larger proportion of the total $CD4^+$ lymphocytes than in lymph nodes. The mid-section of the continuous Peyer's patch in the ileum contained 7% CD4 single positive, 8% CD8 single positive and 4% CD4/CD8 double positive lymphocytes.

2.3.2 Lamina Propria Lymphocytes (LPL)

The gastrointestinal lamina propria is composed of smooth muscle cells, fibroblasts, blood vessels and lymphatics that make up a highly vascular layer of loose connective tissue underlying and supporting the mucosal epithelium. There are macrophages, dendritic cells, neutrophils, mast cells, and lymphocytes that participate in lamina propria effector functions (Hunyady et al., 2000). The population of lymphocytes that resides in the lamina propria has been classified as heterogeneous, and the organization of these cells is classified as random (Bailey et al., 2005). These characteristics are consistent with the effector function of lamina propria lymphocytes, which enables these cells to participate in immunosurveillance and to respond actively to potential pathogens (Burkey et al., 2009). Mixed population of T lymphocytes include helper $CD4^+$ in adult swine settled in lamina propria of the villi and suppressor/cytotoxic $CD8^+$ lymphocytes closer to epithelial cells (Vega-Lopez et al., 1993). The same author found that lamina propria comprise the unique population of $CD2^+CD4^+CD8^+$ lymphocytes (about 30%), as well as $CD2^+$ and $SWC3^+$ (swine workshop cluster) monocyte-granulocyte cells. Important differences in lamina propria lymphocytes exist between humans and swine that may relate to the function of these compartmentalized cells. In the small intestine of pigs, lymphocytes have been categorized as diffuse or organized (Pabst & Rothkotter, 1999). For the most species, intraepithelial lymphocytes and lymphocytes contained in the lamina propria are considered diffuse lymphocytes. In contrast, the gut mucosa of the pig has a greater degree of organization compared with the gut mucosa of rodents and humans (Bailey et al., 2001). For example, Vega-Lopez et al. (1993) observed that plasma cells are preferentially localized to the intestinal crypts and T cells to the intestinal villi. The same authors also observed a spatial separation between $CD4^+$ and $CD8^+$ T cells within the lamina propria of intestinal villi. In addition, researchers have observed differences in cytokines secreted by activated porcine and murine lamina propria T lymphocytes compared with human lamina propria T lymphocytes (Harriman et al., 1992; Bailey et al., 1994). The significance of the differences that exist in pigs has not been fully elucidated. It has been suggested that lamina propria lymphocytes, in addition to their effector function, also have a role in immunoregulation (Bailey et al., 2001). Lamina propria T cells differ from peripheral T cells in that they have a greater threshold of activation, produce increased concentrations of cytokines on stimulation, and have a phenotype associated with immunologic memory (Wittig & Zeitz, 2003).

2.4 Gut cytokines

Cytokines are small peptide molecules derived either from traditionally immune cells (lymphocytes, macrophages) or produced by epithelial cells, endothelial cells and fibroblasts

(Pie et al., 2003). They are powerful mediators that regulate the appropriate host defence against enteric pathogens and other luminal events, and participate in the maintenance of tissue integrity. Cytokines receptors are located on both immune and non-immune cells, and every change in the number, location and distribution of these receptors exert a significant impact on the function of the gut. Syntesis of proinflammatory cytokines can have a strong influence on gut integrity and epithelial functions, permeability to macromolecules and transport of nutrients and ions (McKay & Baird, 1999).

The usefulness of gut immunity depends on tissue integrity, cell function, clinical states, the site of primed immune or others cells. Production of cytokines depends also on mucosal micropopulation. Daudelin et al. (2011) found that expression of IL-8 in the ileum was significantly greater in the pigs challenged with ETEC F4 than in the nonchallenged animals, but IL-8 gene expression was significantly increased with probiotic addition (*P. acidilactici* + *S. cerevisiae boulardii*), compared to the control group. Other *in vitro* studies indicate an increase in IL-8 production following the stimulation of porcine intestinal epithelial cells, Caco-2 cells or a porcine macrophage cell line (3D4/31) with ETEC F4 (Roselli et al, 2006; Pavlova et al., 2008). Probiotic bacteria such as *Bifidobacterium lactis* BB12 stimulated IL-6 production in primary murine intestinal epithelial cells (Ruiz et al., 2005). In addition, this cytokine plays an important role in the regulation of immune intestinal response, barrier fortification, activation of neutrophils and B cell IgA isotype switching (Haller et al., 2000). Similarly, ileal TNF-a gene expression tended to be upregulated in the *P. acidilactici* + *S. cerevisiae boulardii* group in comparison with the control group, which means that the administration of probiotics induced a stronger inflammatory reaction than the feeding of an antibiotic enriched diet (Daudelin et al., 2011). The pattern of cytokine secretion by pig intestinal epithelium depend on the strain of bacteria used (Bailey, 2009). In study by Roselli et al., (2007), *Lactobacillus sobrius* reduced the amount of IL-8 secreted by IPEC-1 in response to ETEC, by stimulation of IL-10 secretion.

There are many reported studies in which feed supplements enhance a component of the immune system. Rodrigues et al., (2007) reported that viable probiotics are more efficient than inactivated probiotics to induce immunostimulation and intestinal modifications in piglets, thus improving their health and development. More IgA expressing cells were found in the mesenteric lymph nodes with the probiotic with viable cells than observed in the inactivated cells treatment. It should be very careful in comparisons and judgments in regard of specific probiotic/prebiotic strains, environment conditions, animal's age and feed composition. Nutrition can also modulate the intestinal cytokine level. Wu et al., (1999) found marked decrease in the levels of IL-10 and IL-4 in mice avoiding enteral feeding.

The roles of gut epithelium are regulation of tissue permeability, absorption of nutrients and ions, secretion and contraction of smooth muscle necessary for mixing contents. Following antigen stimulation, naive $CD4^+$ T cells proliferate and differentiate into various T cell subsets including T helper (Th)1, Th2 and Th17 effectors cells, and T regulatory cells-Treg (Vignali et al., 2008). The development of Th1 cells is the typical response to intracellular pathogens, such as bacteria or viruses. Th1 cells mediate through their secreted cytokines: interferon gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), IL-1β, IL-2, IL-12. Th2 cells are initiated by IL-4 and develop in response to allergens or parasite infection. Cytokines that induce Th2 cells are IL-4, IL-5, IL-13. The third T-effector cell lineage is Th17 subset, which also participate in antimicrobial immunity and inflammatory pathology (Bailey, 2009). Commensal microbial flora drives accumulation of Th17 T cells in healthy, SPF compared to germ-free mice, but numbers and activation state further increase in colitis

(Niess et al., 2008). The differentiation of $CD4^+$ T cells into Trag plays a critical role in maintaining immunological tolerance to self antigen or suppressing excessive immune responses (Vignali et al., 2008). Mucosally activated T cells may differ from systemic T cells better towards interleukin-4 (IL-4) than IL-2, by polyclonal lines from murine lamina propria cells (Bailey et al., 1994). Some cytokines expressed by the intestinal epithelium and have great influence on the epithelial cells growth and homeostasis are TGF-β, IL-1α, IL-6. IL-8, IL-1β and TNF-α upregulated in response to microbial infection. After an ischemic or ischemia/reperfusion type injuries the levels of TNF-α and IL-6 released from the rats' gut (Grotz et al, 1999). The recent study suggests that gut microflora may have adverse effects by modulating gut cytokines, which would alter other components of gut function, and may make the host susceptible to other infectious and metabolic processes. The portal and systemic TNF and IL-6 levels were higher in those rats whose GI tracts were colonized with **E. coli** (bacterial overgrowth) than in rats with either normal intestinal microflora or whose intestinal flora had been decontaminated with oral antibiotics. The disruption of the normal intestinal microflora may result in bacterial overgrowth with enteric bacilli that can subsequently translocate to distant organs and the systemic circulation.

3. Natural products and biological substances as immune response modifiers

Since 2006 the European-wide directives are restricting the non-clinical use of antibiotic growth promoters (AGPs) in food animal production. To accommodate the withdrawal of AGPs it now becomes urgent to provide relevant health criteria and scientifically founded recommendations for alternatives to in-feed antibiotics. Since the 1980's intriguing reports have appeared suggesting that vast variety of substances of natural origin can restore, stimulate or suppress nonspecific and specific immunity in domestic food animals and, hence improve their growth and performance, acting as immune response modifiers (IRMs). The scope of this chapter is to compile recent knowledge on the exogenous immunomodulation of the immune responses in the pig as an important biomedical model. With the growing knowledge of porcine immune system and its endogenous modulation, it has been clarified that exogenous immunomodulation represents an important prophylactic/therapeutic approach aiming at stimulating natural host defenses through the use of a broad spectrum of immunomodulating/growth-promoting agents of a natural origin generally termed IRMs. With combined efforts of basic and clinical veterinary immunologists, animal producers and feed manufacturers, immunomodulation will bring into veterinary medicine, particularly in swine production, the same type of curative revolution as antibiotics have in the combat against infectious diseases. However, it is essential to select fully evaluated IRMs which may act either as nonspecific immunostimulators or synergistically as adjuvants with vaccines. Although, numerous of these substances have been successfully used in *in vivo* nutritional investigations in pig, substantiation of their efficacy is still lacking. Herein we will comparatively analyze immunomodulating properties of some IRMs such as prebiotics, probiotics and immunomodulators (including microbiotics, fungibiotics, phytobiotics and zoobiotics) from several sources applied *in vivo* in different concentrations using domestic swine as a model organism in relation to immunostimulatory effects of some exogenous IRMs of microbial or animal origin tested *in vitro* and *in vivo* on suckling and weaned pigs in our laboratory.

3.1 Early days of IRMs

Since the mid 1980's intriguing reports have appeared suggesting that vast variety of substances of natural or synthetic origin act as IRMs and can restore, stimulate or suppress the innate and adaptive immunity in domestic food animals and, hence improve their growth and performance (Blecha and Charley, 1990). The enormous number of empirical studies of exogenous effects of manipulation of the immune system of the pig by IRMs and feed additives have been carried out (reviewed by Valpotić, 2000; Gallois et al., 2009; Bailey, 2009).

The naturally occurring substances with a long history as immunomodulators are the herb extracts described by Chinese traditional medicine originated from plants *Angelica sinensis* and *Cynachus auriculatus,* which are well known today as IRMs (Weng et al., 1987) or antimicrobials (Kawakita et al., 1987). Today is possible to extract, characterize and classify the substances with putative immunomodulatory properties from different natural sources. Based on their biological or chemical origin bioactive substances with properties of IRMs have been classified by Poli (1984). Further, Reizenstein & Mathe (1984) divided IRMs on the basis of their origin to biological and synthetic substances. Moreover, a number of chemotherapeutics exhibited immunomodulatory activities (Sedlacek et al., 1986). The IRMs of importance for veterinary medicine were further classified into three categories as: physiological products, microbial products and synthetic compounds (Mulcahy & Quinn, 1986). Generally, the IRMs may be divided into substances of endogenous origin, normally produced by the genome of the host and those of exogenous origin which are not products of mammalian genome, but may stimulate production of endogenous IRMs and modulate the immune response of the host (Roth, 1988). The capacity of tested endogenous (neuropeptides, hormones, cytokines, immunoglobulins, peptides) and exogenous IRMs (plant and microbial extracts, synthetic compounds, feed additives, drugs) to improve immune status of laboratory and domestic animal species has been thoroughly reviewed (Wybran, 1988; Georgiev, 1991, 1993; Valpotić, 2000). The synthesis of all these classifications, supplemented with newly emerged bioactive organisms/substances is given in the Table 1.

Origin of IRMs	Type of immunomodulation	Group/source of IRMs	Bioactive molecules/organisms
ENDOGENOUS	Physiological	- hormones - cytokines - acute phase proteins - enzymes - nucleic acids	thymic hormones, lymphokins, monokins, inteferons, TNFα/β, CSF, CRP, haptoglobin, neopterins, NOS, immunogenic RNA/DNA
	Neuroendocrine	- hormones - neuropeptides	ACTH, glucocorticoids, somatostatin, prolactin, TSH, opioids (enkephalin, endorfin, dinorfin, neurotensin)
	Behavioral	- brain-immune system - interactions	neurotrasmitters (VIP, SP), cytokines (IL-1, TNFα, IL6, IL-8), hormones (ACTH, β–endorfin, thyreotropin, cortisol)

Origin of IRMs	Type of immunomodulation	Group/source of IRMs	Bioactive molecules/organisms
EXOGENOUS	Biological	- microbiotics - fungibiotics - phytobiotics - zoobiotics and their products/by-products/derivatives	viruses (Duphamun® – inactivated avipox virus, Baypamun®-inactivated *Parapoxvirus ovis*), bacteria (*P. acnes, E. coli, M. bovis, S. pyogenes, L. casei, S. olivoreticuli, K. pneumoniae), yeasts (S. cerevisiae)* and their derivatives (mannan, glucan), fungi (*T. inflatum, L. edodes, C. albicans, A. bisporus*) and their derivatives (mannan, glucan, lentinan) , plant and algal extracts (carotenoids, flavonoids, polyphenols, saponin, fucan, carvacol, thymol, curcumin, laminarin, phycarin, fucoidan), animal products (bee venom, royal gelly, propolis, fish oil) and animal by-products (colostrum, lactoferrin, spray-dried plasma, purified IgG or total Igs)
	Chemical	- natural compounds - synthetic compounds - metals/microelements	lipopolysaccharide, peptidoglycan, muramil dipeptide, levamisole, POE-POP copolymer, isoprinisine, indometacine, ascorbic acid derivatives, ciprofloxacin, ^{132}Ge organic compounds, organic acids (acetic, benzoic, citric, formic, fumaric, lactic, phosphoric, propionic, sorbic, tartaric), acetic salts (K/Na-benzoate, Na-butyrate/citrate, K-formate/sorbate, Ca-lactate/propionate), Zn, Fe, Cu, Se.
	Nutritive	- nutrients - nutraceuticals	nucleotides, aminoacids (arginine, cysteine, glutamine),carotenoids, flavonoids, n-3 , polyunsaturated fatty acids, vitamins (A and E), minerals (Zn, zeolites)

Table 1. Classification of IRMs based on genetic origin, group/source and type of immunomodulation

TNF = tumor necrosis factor; CSF = colony-stimulating factor; CRP = C-reactive protein; NOS = nitricoxide synthase; ACTH = adrenocorticotropic hormone; TSH = thyroid stimulating hormone; VIP = vasoactive intestinal peptide; SP = substance P; IgG = immunoglobulin G; POE-POP = polyoxiethylene polyoxipropylene

The most common protocol for studies of IRMs effectiveness involves feeding (or application via other routes) the test bioactive substance or compound to young animals, recording feed intake and growth rate as a measures of the efficiency of the animal overall, and recording immunological parameters as direct measures of contribution of the IRMs effect on immunological function. The results from such studies generally fall into two categories. In the first, application of IRMs resulted in an increase in a specific parameter of the immune system. Recently reported studies in which feed supplements enhance a component of porcine immune system have generally focused on increases in IgA, cytokines or serum/intestinal leukocyte subsets. In the second, feed supplementation had no effect or decreased measures of the mucosal immune system. A modification of this protocol is to challenge test and control pigs with a specific pathogen or antigen (including vaccines), where outcomes have been similarly variable (reviewed by Blecha & Charley, 1990; Valpotić, 2000, Gallois et al., 2009; Bailey, 2009).

It should be apparent from the previous discussion regarding modulation of growth and immune functions that the observation of increased, decreased or unchanged measures of these parameters by themselves cannot be interpreted as beneficial or harmful. Each of the studies reports important finding, but an understanding of the mechanisms and, perhaps more importantly, the ability to predict which IRM or feed additive may be beneficial under particular environmental conditions, is going to require many more studies and an overall meta-analysis of the data. The advantage of working with the pig for these studies is that large field trials can be carried out under a range of environmental challenges (intensive, extensive rearing systems) in association with detailed study protocols comprising defined and well characterized IRMs.

Following a brief description of historical aspects on IRMs, we will focus on a group of exogenous bioactive organisms/substances that have been suggested to show immunomodulatory properties, particularly in the pig model systems.

3.2 Nonspecific immunomodulation in swine: A state of art

Unlike specific immunmodulation or vaccination, nonspecific immunmodulation is a complex concept in scientific terms because there is the necessity to balance immunostimulation against excessive activation of the immune system which is usually damaging and growth-inhibiting. Also, certain IRMs when used as immunostimulants are likely to exhibit immunosuppressive effect at increased doses. Clearly a more robust, rapid and sustained immune response would be desirable. Pigs selected for high humoral and cellular immune responses had better growth rates than pigs with low immune responses (Wilkie & Mallard, 1999). In pig production, this is of particular importance during the weaning transition when pigs are subjected to major stressful events, making them highly susceptible to digestive disorders. At that time, the development of both innate and adaptive systemic and local intestinal immunity is critical in preventing the potential harmful effects of pathogenic agents. Strategies aiming at stimulating natural defenses of swine through the use of IRMs able to modulate immune functions have gained increased interest in animal research, and different bioactive components sharing properties of IRMs have been the subject of *in vivo* and/or *in vitro* investigations in pigs (Blecha & Charley, 1990; Valpotić, 2000, Gallois & Oswald, 2008; Gallois et al., 2009).

Nonspecific immunostimulation primarily implies stimulation of the innate or nonspecific immunity which comprises monocytes/macrophages, neutrophils, NK cells, intraepithelial lymphocytes, complement, CRP, haptoglobin and cytokines, such as IFNs, but also certain T- and B-lymphocyte subsets of adaptive or specific immunity. The aim of immunomodulating

substances is to help pigs develop "appropriate/optimal" active responses from both innate and adaptive immunity. However, these substances generally termed IRMs have to fulfill a variety of properties from technical and regulatory viewpoints, but also should share a positive image towards the public (Gallois et al., 2009). Thus, products/derivatives from natural sources will probably be easily accepted by the public and legislation.

3.2.1 The effects of IRMs as natural alternatives to AGP in pig production

Until recently, problems of enteric infections in food animal production have been overcome by adding sub-therapeutic doses of AGPs in-feed to enhance production efficiency in swine industry (Cromwell, 2002). Concerns about potential risks for human health due to use and misuse of AGPs in animal feeds (Dewey et al., 1997) have led to their ban throughout EU (Regulation EC no. 1831/2003). These criteria which are commonly accepted within EU must be usable for objective assessment of alternatives to in-feed AGPs (Gallois et al., 2009) and must be acceptable for swine producers, feed manufacturers and consumers. To accommodate to withdrawal of AGPs it now becomes urgent to provide relevant gut health criteria for a large-scale production of pigs and scientifically founded recommendations for alternatives to in-feed AGPs. More recently focus has shifted from specific immunization to another non-antibiotic approach offered by the use of IRMs, and prebiotics/probiotics in non-specific immune/nutritive stimulation of resistance to enteric infections. Such strategies aiming at stimulating natural host defence through the use of substances of natural or synthetic origin able to modulate immune functions have gained increasing interest in food animal research (Mulcahy & Quinn, 1986; Blecha & Charley, 1990; Valpotić, 2000; Gallois & Oswald, 2008; Gallois et al., 2009). This chapter will focus on groups of in-feed alternatives to AGPs originated from fungi and their derivatives, termed fungibiotics (Table 2), plants and their extracts, termed phytobiotics (Table 3) and animal products and by-products, termed zoobiotics (Table 4) that have been suggested to exhibit immunomodulatory properties and that have been tested in *in vivo* studies in pigs.

A variety of polysaccharides from different natural sources, particularly yeast derivatives β-D-glucans and α-D-mannans (Brown & Gordon, 2003) have been recognized to be responsible for modulating the immune responses in farm animals, including pigs (Table 2) through specific interactions with different immune cells (Kogan & Kocher, 2007). Numerous preparations derived from yeast cell walls, fungi (Table 2), marine algae or plants (Table 3), particularly rich in glucans and mannans, have been investigated in pigs. The BGC extracted from the cell wall of baker's yeast *Saccharomyces cerevisiae* is the most common source used for pig in-feed complements. It is a β-1,3-glucan with long β-1,6-glucan branches, whose structure is different from the β-glucans extracted from bacteria (linear β-1,3-glucans), fungi (short β-1,6-glucans branched β-1,3-glucans) and cereals (β-1,3/1,4-glucans), and thus, their different chemical structures would be expected to be reflected in their different bioactivities (Tzianabos, 2000). Much interest has been paid to the effects of BGC and MOS on porcine systemic immune responses, particularly innate immunity, whereas literature dealing with their effects on local intestinal immunity is very scarce (Table 2). Generally, the effects of BGC on porcine immunity are not predictable and their ability to act as growth-promoters is also not reliable. Their beneficial effects on health were difficult to detect since many of the studies have been performed in "clean" environments where morbidity/mortality rates are low. As for BGC, the influence of MOS on porcine immunity is not always reliable, as well as their effects on pigs performances and health, particularly following challenge infections with enteric pathogens (Table 2).

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Stressor/challenge or vaccinal organism	IRM applied in-feed or *per os*	Effects on immune and production paramet
Weaning	β-glucan polysaccharide (BGC; single oral dose of 100µg or 1mg/pig)	NT; Increased average body weight
Weaning	BGC (0.1%)	None on blood neutrophil function; Lower average daily feed intake; None on average body weight.
Weaning /*Streptoccocus suis* - immunization	BGC (0.025-0.05%)	None on phagocytic function of macrphages/neutro Decreased level of haptoglobin in plasma; Increase of average body weight; Higher average daily feed intake. None on feed conversion.
E.coli vaccine/Partus	BGC (0.05%)	Increased levels of specific colostral/milk antibodies None on no. of liveborn/stillborn pigs; Decreased average body weight; Slower recovery from neonatal diarrheal disease.
Weaning	BGC (0.05%)	Decreased serum level of antibody to F6 antigen or w influence on antibodies to F4, F5 and LT antigens; Increased average body weight; Without influence on incidence of diarrhea.
Weaning	BGC (0.4%)	Increased proportion of $CD8^+$ and decreased propor $CD4^+$ T cells; Decreased no. of granulocytes/monocytes; None on average body weight and average daily fee Decreased incidence of diarrhea.
Weaning	α-mannan oligosaccharide (MOS; 0.1%)	None on blood proportions of $CD4^+$ or $CD8^+$ cells.
Weaning	MOS (0.2%)	Without influence on proliferative response of PBL.
Weaning/$F4^+$ *E. coli* challenge	MOS (3%) from brewer's yeast)	None on serum levels of IgA, IgM and IgG following challenge or without challenge.

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Stressor/challenge or vaccinal organism	IRM applied in-feed or *per os*	Effects on immune and production parame
Weaning/ *Salmonella enterica* - challenge	MOS (0.15%)	Increased serum concentration of haptoglobin; None on serum level of Il-6; Without influence on hyperthermia after challenge i None on growt performance.
Weaning	MOS (0.3%)	Without influence on no. of intestinal macrophages; Increased phagocytosis of macrophages from JLP. Lowered ratio of $CD3^+$ $CD4^+$/$CD3^+$ $CD8^+$ blood T ce a higher proportion of $CD8^+$ T cells. Decreased no. of blood neutrophils.
Weaning	MOS (0.2- 0.3%)	Decreased proliferative responses of PBL to PWM o
Weaning/PRRS virus - vaccination	BGC (0.015-0.03%)	Tendency of serum haptoglobin increase; None of lymphocyte proliferation; Without influence on increase in level of specific ant PRRS virus; None on average body weight and feed conversion; Increased average daily feed intake.
Weaning/ Ovoalbumin - or LPS - immunization + LPS *in vitro*	BGC (0.005%)	Short-term increase of humoral immunity to ovoalbu Increased release of IL-10, and decreased IL-6 and TN production after *in vitro* or *in vivo* stimulation of PBL NT.
Weaning/LPS - immunization	BGC (0.005%)	Increased plasma levels of IL-6, TNFα and IL-10; Without influence on somatotropin level.
Weaning	BGC (0.005%)	Decreased reactivity of PBL to PHA or ConA mitog Increased average daily feed intake and body weigh None on feed conversion.
Weaning/Atrophici rhinitis – vaccination + in-feed antibiotics	BGC (0.02-0.04%)	Slightly changed level of antibody specific for *Paste* *multocida* sv. A and D; Increased proportion of $CD4^+$ and tendency of incre proportion of $CD8^+$ PBL; Increased average body weight; Better feed digestibility.

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Table 2. *In vivo* immunomodulatory effects of dietary supplementation of fungibiotics on porcine immune and production parameters

Weaning = from 2-4 weeks; BGC = β glucans given either in diets or orally originated from bakers yeast *S. cerevisiae* ,except where sources were given in parenthesis; LT = thermo labile toxin, PRRS = porcine reproductive and respiratory syndrome; PWM = pokeweed mitogen; PHA = phytohaemagglutinin, ConA = concanavalin A; NT = not tested

Stressor/challenge or vaccinal organism	**IRM applied in-feed or *per os***	**Effects on immune and productio**
Weaning/LPS - immunization	BGC (2.5%)	Increased intestinal TNFα and IL-1β, b receptor antagonist mRNA; None in blood TNFα level and leukocy
Weaning	MOS (0.1%)	Reduced recruitment of lymphocytes i lamina propria; Profiles of intestinal and PBL subsets i
Weaning/F4+ ETEC - immunization	BGC (0.05%); from fungus *Sclerotium rolfsii*)	Decreased serum level of antibody to I Increased numbers of IgM^+ and IgA^+ p JPP/IPP, and decreased in MLN; Lower susceptibility for $F4^+$ ETEC infe Lower incidence of fecal isolates of F4 Milder or totally reduced diarrhea.
Weaning/ *S. enterica* sv. Typhimurium - immunization	BGC (0.2%)	NT; None on average body weight; Lower incidence of *S.enterica* sv. Typhi feces:
Weaning/$F4^+$ ETEC - immunization	Yeast fermentation product (0.2% XPC®) from *S. cerevisiae*)	Increased PCV of blood leukocytes; Increased average daily feed intake, Smaller no. of adherent ETEC to ileal r Decreased no. of *Eneterobacteria* in ileal Improved growth and gut health statu

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Stressor/challenge or vaccinal organism	**IRM applied in-feed or *per os***	**Effects on immune and production paramet**
Weaning*/ *S. enterica* sv. Typhimurium - immunization	Fucan polysaccharide (0.5-2.0%) from seaweed *Ascophillum nodosum*)	Increased feed intake, but decreased feed efficiency; Without influence on immune responses; Challenge infection had only moderate effects on pigs; Increased activation of alveolar macrophages to secrete prostaglandin E2 (PGE2); None on secretion of IL-10 by splenocytes.
Weaning/ *S. enterica* sv. Typhimurium - immunization	Saponin (0.0125-0.05%) from *Quillaja saponaria*)	Without influence on feed intake and growth rate follow challenge infection with *S. enterica;* None o serum levels of haptoglobin, α-1-acid glycoprote postinfection; Slightly weaker phagocytic function of blood leukocytes higher dose of saponin.
Weaning	Saponin/Curcumin (0.02-0.03%) from *Q. saponaria/Curcuma longa*)	Without influence on immune response (curcumin); Increased concentrations of IgA, IgG and CRP (saponin) Decreased feed : weight gain ratio and, thus, feed utiliza Improved health status of pigs.
Weaning	Carvacol, thymol (0.3%) from *Cinnamomum spp*., *Capsicum annum* and Oregano feed additive™)	Increased proportions of $CD4^+$, $CD8^+$ and $CD4^+$/ $CD8^+$ T peripheral blood and MLN Protection of low-weight pigs from disease.
Weaning	Sugar cane extract - polysaccharides ?) (0.5-2.0g/kg of BW) from *Saccharum officinarum*	Increased NK cell cytotoxicity and phagocytosis of monocytes/neutrophils; Low morbidity and mortality rates.
Weaning	Chicory acid, alkamids (1.8 cobs for 6 weeks) from *Echinacea purpurea*)	None on growth performance; Slightly increased feed efficiency; Nonaffected blood parameters – cell count and prolifera Improved health status of pigs;

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Stressor/challenge or vaccinal organism	IRM applied in-feed or *per os*	Effects on immune and production paramet
Weaning/ *Erysipelothrix rhusiopathiae* - vaccination	Chicory acid, alkamids (1.5 cobs and 4-6 ml juice/day for 9 weeks) from *E. purpurea*	Enhanced response to vaccine against *Erysipelothrix rhus* Increased serum level of specific antibody.
Weaning/LPS - immunization	BGC (0.05-0.1%) from Chinese herb *Astragalus membranaceus*)	Increased plasma levels of IL-1β, PGE2 and cortisol; Enhanced reactivity of PBL to ConA; Increased production of IL-2 following the immunizatio None on average body weight and feed conversion; Decreased average body weight after immunization wit Increased average daily feed intake; Higher plasma level of glucose. Increaed plasma levels of IL-1β and PGE2 after LPS imm
Weaning/Ovoalbumin - immunization	BGC (0.01-0.1%) from *A. membranaceus)*	Incresed blood leukocyte count; Increased proportion of $CD4^+$ T cells; Increased blood concentrations of IL-2 and IFNγ follow immunization; Non-affected levels of IL-4 and IL-10; None on specific antibody titers following immunizatio ovoalbumin.
Weaning	Carvacol, cinnamaldehyde, capsicum oleoresin (0.03%) from *Origanum spp.*)	None on subsets of mononuclear cells from IPP; Decreased percentage of B cells in ileal/colonic lymph n
Weaning	Carvacol, thymol (0.05-0.15%) from Phytogenic™ additive)	Without influence on plasma levels of CRP and haptogl

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Table 3. *In vivo* immunomodulatory effects of dietary supplementation of phytobiotics on porcine immune and production parameters
* At 2-4 weeks of age; BW = body weight; NK = natural killer; SRBC = sheep red blood cells. BGC= β glucans

Stressor/challenge or vaccinal organism	**IRM applied in-feed or *per os***	**Effects on immune and production pa**
Weaning/LPS or Ovoalbumin-immunization	Flavonoids, polyphenols (1%) from Bahzen™ Chinese herbal medicine)	Increased blood leukocyte count; Enhanced release of serum IL-6 and TNFα f LPS immunization; Increased levels of blood IgG and activity o neutrophils; Without influence on specific antibody resp SRBC or ovoalbumin; Improved growth rate.
Weaning	BGC (0.15%) from brown algae *L. digitata* and/or *L. hyperborean)*	Increased expression of mRNA for IL-8; Increased no. of monocytes; Decreased no. of enterobacteria, bifidobact lactobacilli in colon/cecum; Lowered height of intestinal vili in duodenum/jejunum.
Level of gases in fattening unit	BGC (?) from barley and oats – diets (13.5MJ/kg) with either or with their combination	NT; Lower digestibility of feed; Increased no. of *Bifidobacterium spp*. and *Lac* in colon; Decreased concentration of ammonia.
Weaning/LPS-immunization	Laminarin (300 or 600 parts/million ppm) from *L. digitata*)	Increased IL-6 and IL-8 gene expression in c following LPS immunization; Reduced population of *Enterobacteria* in colo Increased expression of mucin genes in ileu

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Seaweed extracts are known to have immunomodulatory properties on the immune parameters in mice (Vetvicka & Ivyn, 2004) and pigs (Reilly et al., 2008; Leonard et al., 2010). Empirical evidences suggest that plant extracts may also offer benefits in stimulating the immune system, and thus, preventing disease in monogastric food animals (Wenk, 2003). A variety of plant-derived products have gained increasing interest as potential feed additives for poultry and swine (Windisch et al., 2008). Plants, and their bioactive components, are very diverse and their potential to enhance pig immunity and health has only been scarcely tested *in vivo* (Table 3).

The most of these studies have used a mixture of compounds (Kommera et al., 2006; Manzanilla et al., 2006), which does not allow the investigation of the immunomodulating properties of a specific bioactive component. However, Chinese pharmacopoeia describes the use of numerous herbal formulations to cure wide variety of diseases. Among those, Bahzen is a medicine composed of eight different plants (*Atractylodes ovata, Codonopsis pilosula, Poria cocos, Glycyrrhiza uralensis, Angelica sinensis, Ligusticum chuanxiong, Paeonia albiflora and Rehmannia glutinosa*) whose extracts have been tested *in vivo* in pigs (Lien et al., 2007). In spite positive image of medical plants in the public opinion a lack of data on the bioactive components of particular plants and the large diversity of their species, it has proved difficult to prepare extracts of equivalent potency, and thus the results of investigations on their influence on pig immunity remains inconclusive.

The most promising results among IRMs tested have been obtained with animal by-products of commercial slaughtering facilities such as purified porcine Igs or IgG (Valpotić et al., 1989a, b) and spay-dried porcine/bovine plasma (Coffey & Cromwell, 2001), whose positive effects would be provided by specific allogenic/xenogenic antibodies as well as by non-specific competition of glycan moieties of plasma glycoproteins with bacteria for intestinal receptors (Table 4). Namely, plasma from both porcine and bovine origins are characterized by a rich protein content, whose Igs can represent 24% to 25% (Niewold et al., 2007), and the IgG fraction would appear to be the main component responsible for the growth-promoting properties (Pierce et al., 2005). The major positive effect of animal product such as bee glue or propolis given in-feed (0.2%) is in reducing numbers of air-born bacteria in pig facilities (Bevilacqua et al., 1997) and the colonization of intestinal mucosa of weaned pigs by potentially harmful bacteria (Špoljarić, personal communication). The effects of spray-died porcine plasma (SDPP) on local intestinal immune responses have been widely studied in pigs (Table 4) and are concordant that SDPP prevents infiltration of GALT by immune cells and decreases jejunal proinflammatory cytokines, reflecting a lower antigenic challenge and suggesting that SDPP would be efficient in helping pigs fight against enteric infections (Jiang et al., 2000; Bosi et al., 2004; Nofrarias et al., 2006, 2007). Concerning systemic immune responses, a supplementation of the diet with SDPP did not modulate blood immune cells (Jiang et al., 2000; Nofrarias et al., 2006, 2007) or cytokines under basal conditions (Touchette et al, 2002), but when immunized with LPS, SDPP-fed pigs showed increased serum levels of proinfammatory cytokines associated with severe intestinal damage, suggesting that these pigs would be more susceptible to certain immunological challenges (Touchette et al., 2002). The growth-promoting properties of plasmas are more commonly observed with SDPP than from with that from bovine origin (vanDijk et al., 2001). The health-promoting properties of SDPP in pigs perorally challenged with an ETEC strain are usually reported as reduction in incidence/severity of postweaning diarrhea and growth promotion (Bosi et al., 2004; Niewold et al., 2007). Bovine colostrum has been shown to enhance intestinal mucosa restoration by stimulating migration of enterocytes and by decreasing apoptosis of apical epithelial cells in weaned pigs (Huguet et

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Stressor/challenge or vaccinal organism	IRM applied in-feed or *per os*	Effects on immune and production parameters
Partus/weaning*	Porcine plasma Igs (single peroral dose of 10 mg/pig or pretreatment of PBL with a same dose)	Increased reactivity of PBL from suckling pigs to PHA a T- mitogen; Decreased reactivity of PBL from suckling pigs to PWM a mitogen; Non-affected reactivity of PBl from weaned pigs to PHA, C PWM; Better survival of during preweaning period.
Microbial load/ population density of pigs	Propolis (vaporized in farm facility)	Reduced no. of CFU in the air; Improved health of weaners.
Weaning	Spray-dried porcine plasma (SDPP; 10%)	Decreased infiltration of GALT by macrophages and lymp None on blood leukocyte count; Promotion of growth.
Weaning/LPS-immunization	SDPP (7%)	None on serum IFNγ or TNFα levels; Increased serum IFNγ or TNFα levels following immuniza with LPS; Severe damage of intestinal mucosa.
Weaning(LPS-immunization	SDPP (7%)	Increased serum Il-6 and Il-1β following immunization wit Without influence on mRNA cytokine levels in liver, thym spleen; Decreased serum CRP, but not haptoglobin level.
Weaning/$F4^+$ ETEC-challenge	SDPP (6%)	Decreased expression of proinfammatory cytokines IL-8 ar Lower serum IgA level; Lower histopathologic score due to a better defense agains infection. Increased average body weight.
Weaning/$F4^+$ ETEC-challenge	SDPP (7%)	None on serum IL-6 level; Prevention of growth retardation and clinical signs of diar disease.

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Table 4. In vivo immunomodulatory effects of dietary supplementation of zoobiotics on porcine immune and production parameters
* At 2-4 weeks of age; SDPP= spray dried porcine plasma; CFU = colony forming units; IFN = interferon; IL = interleukin

Stressor/challenge or vaccinal organism	IRM applied in-feed or *per os*	Effects on immune and production pa
Weaning	SDPP (6%)	Decreased infiltration of GALT by immune cell None on no. of blood leukocytes; Promotion of growth.
Weaning	SDPP (6%)	Decreased infiltration of GALT by immune cell None on no. of blood leukocytes; Increased average body weight..
Weaning/Rotavirus + $F4^+$ ETEC- challenges	SDPP (8%)	Reduced postweaning diarrhea and increased g Increased specific antibody against LT of ETEC Decreased ETEC excretion. Competition of glycan moieties of glycoprotein with intestinal receptors for F4 fimbrial antigen
Weaning	Bovine colostrum (1g or 5g/day/pig for 3 weeks)	Increased profiles of IL-2, IFNγ and IL-12 (Th1) IL-10 cytokines (Th2) in IPP (more Th2 than Th More pronounced Th1 profile of cytokines in JL Decreased total no. of mononuclear cells in IPP proliferative responses were increased; Decreased $CD21^+$ cell count and increased CD3 subset 3 weeks postweaning; Systemic immune responses non-affected.
Weaning	Lactoferrin (0.1%)	Increased blood level of IL-2 and C4 componen complement; None on IL-1α or C3 blood concentrations; Enhanced proliferation of PBL and splenocytes with PHA or ConA; Increased serum levels of IgG, IgA and IgM, Prevention of diarrhea.
Weaning	SDPP (2.5 or 5.0%)	Decreased level of TNFα in colon, but not in ile Decreased level of IFNγ in ileum and colon; Reduced diarrheal disease.

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3.2.2 Croatian experiences with IRMs in veterinary medicine

In the following, the capacity of selected natural substances of microbial, fungal and animal origin to improve performances and the immune status of swine is reviewed based on *in vivo* or *in vitro* investigations performed in Croatian scientific community (Table 5). In our opinion, two main reasons are responsible for this research interest of a group of veterinary immunologists in Croatia: (i) at that time (the end of 1980') literature dealing with IRMs as natural alternatives to in-feed AGPs and their impact on porcine immunity was scarce, and (ii) more recently (since 2006 in the EU) the total ban of in-feed AGPs and trends in research work on that topic may arise in the following years.

Indeed, to accommodate to withdrawal of AGPs it now becomes urgent for Croatia as a member candidate and for Croatian scientific community to follow-up forthcoming EU regulations and keep-up with scientific trends in veterinary immunology in order to provide relevant health criteria and scientifically founded recommendations for alternatives to in-feed AGPs.

For each type of substance, only major elements concerning experimental designs, such as the immune/performance parameters which have been studied by differentiating the systemic and local intestinal immune responses were given. In spite of the fact that in most of the experiments *in vivo* application of IRMs has been performed parenterally, the gut mucosal immune cells have been prevalently studied. Thus, immune reactions after such applications of natural IRMs cannot directly be linked to a defined site of origin. So far, it is often difficult to explain whether their reaction pattern depends on intestinal mucosal or systemic immune responses. However, intestinal mucosal immune responses can occur independently of systemic immunity (Hannant, 2002).

Considering experimental designs in the context of testing IRMs (Table 5) it is necessary to mention that in the most cases stressful events such as birth and weaning (accompanied with ETEC challenge and non-ETEC vaccination) have been used as a model systems. To help pigs to cope with postweaning transition, various nutritional approaches have been proposed, including supplementation the diet with substances that increase appetence or have anti-microbial and/or immunostimulating properties (Lalles et al., 2007). Amongst the alternatives to in-feed AGPs, the IRMs, including preparation of inactivated *Parapoxvirus ovis* (Valpotić et al., 1993; Grgić et al., 1995; Šver et al., 1996a; Krsnik et al., 1999, Šperanda et al., 2008) and yeast derivatives such as Progut® (mixture of α-mannans, β-glucans, nucleotides and peptides) and BioMOS® (α-mannan oligosaccharide) are attracting greater attention (Šperanda et al., 2008, Valpotić, 2009; Špoljarić et al., 2011). Indeed, the correct functional development of the gut and GALT is of crucial importance in controlling potential pathogens during neonatal and postweaning period. Weaning affects the ontogeny of immune functions, largely as a consequence of the withdrawal of milk and catabolism of colostral antibodies, which have important implications for passively modulating immune responses through both suppressive and enhancing pathways. In accordance with this phenomenon, plasma-derived porcine IgG acted *in vitro* as an IRM on PBL reactivity to T- or B-cell mitogens from weaned pigs (Valpotić et al., 1989).

Finally, to assess the impact of in-feed IRMs simultaneously on immunity and on performances and health, the pigs used in these experiments (Table 5) were kept under commercial farm conditions implying that they were exposed to immune/infectious challenges. Thus, the studies performed may reflect immune functions and dysfunctions occurring following exogenous immunomodulation.

Stressor/ challenge or vaccinal strain	IRM applied		Effects on immune and production pa
	in vivo	*in vitro*	
Partus	-	PGM	Increased no. of macrophages and decr proliferation of PBL; Better survival of
Partus/weaning*	-	Porcine IgG**	Increased T and decreased B cell prolife
Weaning	-	PGP	Increased no. of leukocytes/lymphocyt
Weaning	-	PGP or PGM	Increased proliferation of PBL/splenoc
Partus	BPM	-	Enhanced lacteal/colostral immunity i primiparous sows/neonatal pigs; Decreased mortality of pigs from litters
Weaning/F4ac$^+$ ETEC or non-ETEC strains	BPM	-	Increased proliferative responses of lym from IPP and MLN
Weaning/F4ac$^+$ ETEC strain	BPM	-	Increased proliferative responses of lym from JLP, IPP and MLN; Increased no. of CD2a$^+$ and CD8a$^+$ T ce
	-	LPS	Increased proliferative responses of lym from GALT
Weaning/ F4ac$^+$ non-ETEC strain 2407	BPM		Higher level of total protein and IgG Incresed no. of leucocytes and share of neutrophils/lymphocytes
Weaning/F4ac$^+$ F6$^+$ ETEC strain	-	MDP	Increased no. of CD21$^+$ B cells in MLN
Regrouping***	BPM	-	Decreased no. of stillborn pigs
Weaning	PGT	-	Increased growth rate; Non-affected no. of blood neutrophils; Increased proportions of CD4$^+$ and CD Increased no. of PBL.
Weaning	MOS	-	Increased proportion of CD45$^+$, CD4$^+$, C CD21$^+$ PBL; Increased no. of CD45RA$^+$ lymphoid ce and IPP; Enhanced phagocytosis of gra

Table 5. Immune and production parameters in conventionally reared pigs following in vivo or in vitro treatment with exogenous IRMs of either microbial origin or fungibiotics/zoobiotics
*At 4-weeks of age, **Purified from swine plasma, ***Primiparous/multiparous sows; PGM/PGP = peptidoglycan monomer/polymer from cell wall of *Brevibacterium divaricatum*; PBL = peripheral blood lymphocytes; BPM = Baypamun® (inactivated *Parapoxvirus ovis*); IPP = ileal Peyer's patches; MLN = mesenteric lymph node; ETEC = enterotoxigenic *E. coli* strain; JLP = jejunal lamina propria; LPS = lipopolysaccharide from cell wall of *Escherichia coli*; GALT = gut-associated lymphoid tissues; MDP = muramyl dipeptide synthetic analogue of molecule from Wax D component of plasmatic membrane of mycobacteria; MOS = mannan oligosaccharide from cell wall of *Saccharomyces cerevisiae* ; IFA = interfollicular areas

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4. Conclusions: Potentials and limitations

Considerable efforts have been focused to understanding of enteric infectious diseases, their diagnosis, including biology of pathogens, host resistance and therapy in intensive large-scale production of food animals, particularly pigs. Conversely, little is known on prevention of such diseases through immunomodulatory and dietary strategies because these problems have been overcome thus far by adding sub-therapeutic doses of AGPs in-feed in swine industry to enhance production efficiency. The AGPs were used not only to improve growth but also to control enteric infections during critical periods such as birth and weaning. Numerous reports have suggesting that vast variety of substances of natural origin termed IRMs, including bioactive components of feed, *i. e.* nutraceuticals (prebiotics, probiotics, minerals) and of organisms, including their products or derivatives, *i. e.* immunomodulators (microbiotics, fungibiotics, phytobioticy, zoobiotics) can modulate (stimulate, suppress or restore) nonspecific and specific immunity in young pigs. Such strategy underlying pharmacological manipulation of the immune system, *i. e.* immunomodulation is to identify parameters of the host response that will indicate enhancement/suppression or restoration to a level of an "optimal immune response", to allow the host better combat against invading microbes during the course of infection. With growing knowledge of porcine immune system and its endogenous modulation, it has been stated in the literature that exogenous modulation using broad spectrum of IRMs represents an important prophylactic/therapeutic approach in prevention/treatment of both stress- and microbial-induced disorders accompanied birth or weaning, particularly enteric infections. Such substances should be effective in protection of gut health, and at same time harmless for animal and environment, and should be capable of stimulating/restoring of gut physiological and immune functions, and thus, could be particularly important during development and maturation of intestinal mucosal immune system. However, it is essential to select fully evaluated agent which may act either as an IRM or synergistically as an adjuvant with vaccines.

As highlighted in this chapter, substances whose immunomodulatory properties often issue from *in vitro* studies are not exhibiting putative potentials when tested *in vivo*, particularly as feed additives. Namely, studies where variety of IRMs (such as yeast derivatives or plant extracts) have been fed to pigs have shown inconsistent results, suggesting that their ability to target particular immune cells through the oral route is questionable. The main causes are: the influence of environment, feed content, present commensals, possible inflammation or ischemia type injuries, which may shift the mucosal immune response as well as the whole gut functions. Consequently, influence of IRMs on pig immunity remains inconclusive. The most promising results to date have been obtained with animal by-products and precuts, such as spray-dried plasma or propolis, respectively. The heterogeneity of these experiments can partly explain the discrepancies on their efficacy due to: (i) variable composition of feed additives, (ii) different time of supplementation, (iii) diversity of experimental designs or measured parameters, and (iv) the level of additive in the final diet often remains unknown as well as (v) the composition of additive itself is not revealed/defined. Moreover, while the effects of in-feed IRMs on systemic immunity are quite well documented, the local intestinal immune responses have only receive little attention despite the fact that the study of systemic immune responses may not reflect immune functions following dietary treatments with IRMs occurring in the GALT. In spite of all these experiments in the context of testing immunomodulatory compounds of various

origin, one main problem is to define what "optimal" immune functions should be targeted. For instance, if there is evidence that immunosuppressive effect is expected to prevent potentially damaging immune-mediated reactions, such as chronic inflammation, stimulation of the active immunity is not required for development and education of the immune system. This is particularly true for GALT where a homeostatic balance has to be reached to both tolerate harmless antigens from commensal bacteria or diet, and eliminate harmful antigens from pathogenic microbes. The definition of an "optimal" immune function is thus highly complex, and in the context of food animal production, it could be defined as the one that offers both the best growth and health status to animal. This, however, implies that pigs are exposed to normal commercial rearing conditions in which they are submitted to immune/infectious challenges in order to objectively assess the impact of in-feed IRMs simultaneously on immunity and on performances and health.

In the future, the effects of in-feed/oral additives on the development of immune responses in the GALT should be more largely documented, as their effects are mainly expected in this compartment. Thus, such studies should include:

- well characterized relevant model systems of young pigs on multidisciplinary basis, and usable for an uniform evaluation of their performances, gut health criteria and optimal functioning of the GALT;
- fully defined IRMs, particularly their bioactive substance(s);
- pharmacokinetic studies intended to know the fate of these substances in the organism, in order to precise their site of action and physiological/immunological effects;
- scientifically founded statement regarding relationship between immunomodulatory effects induced by dietary IRMs and health status of pigs, as the final goal of using such substances in pig nutrition is to promote their performance, health and welfare.

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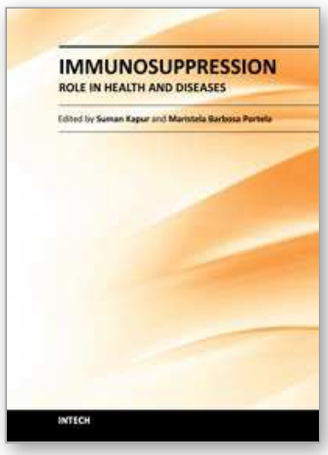
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A need for a book on immunology which primarily focuses on the needs of medical and clinical research students was recognized. This book, "Immunosuppression - Role in Health and Diseases" is relatively short and contains topics relevant to the understanding of human immune system and its role in health and diseases. Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Therapeutic immunosuppression has applications in clinical medicine, ranging from prevention and treatment of organ/bone marrow transplant rejection, management of autoimmune and inflammatory disorders. It brings important developments both in the field of molecular mechanisms involved and active therapeutic approaches employed for immunosuppression in various human disease conditions. There was a need to bring this information together in a single volume, as much of the recent developments are dispersed throughout biomedical literature, largely in specialized journals. This book will serve well the practicing physicians, surgeons and biomedical scientists as it provides an insight into various approaches to immunosuppression and reviews current developments in each area.

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