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Session 6: Role of physical activity on immune function Diet, exercise and gut mucosal immunity

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Diet and exercise are primary strategies recommended for the control of the obesity epidemic. Considerable attention is being paid to the effect of both on the immune system. However, little research has been done on the effect of diet, nutrients or exercise on the mucosal immune system. The gastrointestinal tract (gut) is not only responsible for the entry of nutrients into the organism, but also for triggering the primary immune response to orally ingested antigens. The gut-associated lymphoid tissue contains a large amount of immune cells, disseminated all along the intestine in Peyer's patches and lamina propria. Specific nutrients or their combinations, as well as the microflora, are capable of modulating the immune system through cell activation, production of signalling molecules or gene expression. We have observed an increase in T-cells as well as a decrease in B-cells from Peyer's patches, induced by diets high in fats or carbohydrates in Balb/c mice. It has also been demonstrated that exercise modulates the immune system, where moderate levels may improve its function by increasing the proliferation of lymphocytes from various sites, including gut-associated lymphoid tissue, whereas exhaustive acute exercise may cause immunosuppression. High-fat diets combined with exercise are able to induce an increase in CD3+ lymphocytes due to increased CD8+ cells and a decrease in B-cells. Explanations and consequences of the effects of diet and exercise on the gut mucosal immunity are still being explored.

Diet: Exercise: Gut mucosal immunity: Obesity

The present obesity epidemic and its related diseases, such as diabetes, hypertension and CVD, among others, have forced the focus of science, and particularly nutrition, on the need to change the lifestyles of the world's population. The recommended changes refer specifically to decreases or adjustments to the diet as well as increases in physical activity, aiming to decrease body weight and improve general health. However, these are only visible consequences and it is to be expected that many other systems will also be affected. It is well known that specific nutrients act as immune-modulators triggering differential responses by adequacy, deficiency or excess; physical activity has also been found to modulate the immune system. However, not much is known about the combined effect of diet and exercise particularly in relation to the mucosal immune system. Here, we review the information related to the gastrointestinal tract (gut) mucosal immune system.

The gut mucosa

The gut is the largest internal surface in touch with microorganisms, starting with the oral cavity, which is considered the most heavily infected site. Due to the large mucosal surface of the gut, it is highly prone to infections,

Abbreviation: gut, gastrointestinal tract.

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containing a great amount of secondary lymphoid tissue, such as the tonsils, adenoids, appendix and Peyer's patches (found particularly in the intestine). Tonsil and adenoid immunity are directed specifically to respiratory infections, while appendix and Peyer's patches are specific for gastrointestinal infections[1].

The intestine has a surface of approximately 300 m^2, dedicated to digestion and absorption of nutrients and mostly any other cell or substance that passes through, including micro-organisms and antigens[2]. Gut-associated lymphoid tissue is the largest lymphoid organ in the human body, containing about 70% of all immune cells (10^6 lymphocytes per gram of tissue). It can be divided into inductor sites, including Peyer's patches, mesenteric nodes and isolated lymphoid follicles; and effector sites such as lamina propria and epithelium[3–5].

Once absorbed, antigens are transported at the inductor sites to macrophages, B-cells and dendritic cells for antigen presentation, migrating through lymph vessels to the nearest lymph node, where they stimulate T-cells to regulate the immune response[6]. Although gut-associated lymphoid tissue cells are peripherally disseminated, they always return to the gut[7]. Once T-helper cells have been activated, they differentiate into T-helper cell type 1, T-helper cell type 2 or the recently described T-helper cell type 17, based on their cytokine production[8].

The most important inductor sites are Peyer's patches, which are easily identifiable conglomerates of lymphoid follicles in the intestine, separated from the lumen by epithelial cells known as M cells, under which are found dendritic cells and macrophages. They have a B-cell follicle with a germinal centre surrounded by T-cell areas, very similar to the anatomy of a lymph node including only efferent vessels. The follicles in Peyer's patches have secretory IgA producing plasma cells[8,9]. Peyer's patches are essential for the induction and regulation of intestinal IgA immunity against oral antigens as IgA isotype switching occurs only in the organized mucosa-associated lymphoid organs[10,11].

The lamina propria is an effector site found between the epithelium and the mucosa muscularis, which contains mature IgA producing plasmatic cells, T-helper cells, macrophages, dendritic cells and mastocytes; these are in constant differentiation, renovation and migration[6,8].

Thus the gut, apart from being the point of entry for nutrients is a very important site for triggering the primary immune response; modifying its characteristics or function can alter the whole systemic response not only to orally ingested antigens, but also to any other type of antigen.

Nutrition and the immune system

The relation between nutrition and the immune system has been studied for a long time. It has been demonstrated that specific nutrients or nutrient combinations may affect the immune system through the activation of cells, modification in the production of signalling molecules and gene expression. This is not only a systemic effect, but is also found and may be even greater in the mucosal immune system[12,13].

For example, much attention has been given to the effect of dietary lipids on lymphocyte proliferation, cytokine production, phagocytic activity, adhesion molecule expression and natural killer cell activity. Various authors have concluded that modification of *n*-3 and *n*-6 PUFA intakes may be beneficial for the immune system through the regulation of inflammatory mediators such as eicosanoids, which are produced as part of the normal immune response[14–16].

With respect to the gut mucosal immunity there is an apparent effect of signalling molecule expression in the epithelial cells induced by changes in the lumen caused by diet or flora. For example, bacterial fermentation induces the production of SCFA, increasing IL-8 production and decreasing chemotaxis[17,18]. The gut epithelium is capable of distinguishing between pathogenic and non-pathogenic flora. Apparently, macrophages in the lamina propria switch off the primary inflammatory response triggered by the epithelium; in some cases transforming growth factor-β may be initiating the tolerance process against non-pathogenic bacteria[19]. It has been demonstrated in animal models that the presence of intestinal flora modulates B- and T-cell proliferation in Peyer's patches and mesenteric lymph nodes in a murine model[20].

Our group has studied the effect of 9 weeks of feeding diets high in fat or carbohydrate on T-cells from lamina propria in Balb/c mice, where we found that both diets increase production of IL-2, IL-5 and TNFα, although the high-fat diet decreased total T-cell population and the high-carbohydrate diet increased this type of cells[21]. The same model was used to study the effect of diet on B and IgA+ lymphocytes in lamina propria and Peyer's patches. High-fat and high-carbohydrate diets decreased CD19+ cells and increased IgA+ cells in both types of tissues[22]. These results (Table 1) indicate that dietary modifications are capable of modulating the local immune response in the gut mucosa.

It is clear that diet as a whole, as well as specific nutrients, may be acting as immunomodulators at all levels. We hypothesise that this is more so at the gut mucosa, due to its closeness in the process of absorption.

Obesity and the immune system

Obesity has been associated with immunosuppression due to an increased susceptibility to infections, increased allergic reactions and poor antibody response to vaccines. These effects are most probably induced by imbalances in the production of obesity-associated hormones, such as adipocytokines, which may be acting as immunomodulators. One of the main features of obesity related to the immune system is the low-grade inflammation as measured by pro-inflammatory cytokines, such as TNFα, IL-1β and IL-6, which are produced by adipocytes as well as by other cell types and are present in various levels of the gut[23].

Leptin is an anorexigenic protein with a structure that places it in the family of the cytokines, produced by adipose tissue proportional to adipose tissue mass. Infectious

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Table 1. Cell populations determined by flow cytometry in peripheral blood, lamina propria and Peyer's patches in Balb/c mice on a high-fat or high-carbohydrate diet*
(Mean values (%) and standard deviations)

	Control		Carbohydrate		Fat		
Cell type	Mean	SD	Mean	SD	Mean	SD	*P*
Peripheral blood							
CD3	12·40	1·42	18·10	1·51	17·31	1·53	0·0001
CD4	50·86	1·41	56	2·46	57·64	3·41	0·063
CD8	11·45	1·14	12·42	0·870	15·64	1·25	0·0001
CD19	26·49	2·98	18·24	2·76	16·21	2·89	0·0001
IgA	0·573	0·261	2·38	1·09	1·27	0·452	0·0001
Lamina propia							
CD3	44·34	3·84	56·36	6·76	30·92	3·62	0·0001
CD4	19·98	3·59	20·24	4·5	1·48	0·333	0·0001
CD8	22·29	3·82	26·93	4·67	3·46	1·87	0·0001
CD19	15·71	2·87	9·09	2·52	6·94	1·50	0·0001
IgA	22·66	0·918	45·57	5·59	31·42	5·36	0·0001
Peyer's patches							
CD3	21·91	1·54	6·21	0·885	10·09	2·77	0·0001
CD4	21·50	1·72	34·40	2·01	34·03	4·21	0·0001
CD8	4·01	1·24	5·85	0·667	7·19	0·432	0·0001
CD19	69·23	2·29	43·30	6·54	50·69	6·06	0·0001
IgA	23·69	2·47	38·72	5·24	59·05	7·66	0·0001

*Statistical analysis by ANOVA.

processes and inflammation cause an increase in leptin synthesis, whereas its deficiency is associated with high susceptibility to infections and an imbalance in cytokine production. Leptin regulates T-cell responses by enhancing TNFα, IL-6 and IL-12 synthesis, thus polarizing the response towards a T-helper cell type 1 pattern, apparently by acting on the long isoform of its own receptor expressed on T lymphocytes[24–26].

Ghrelin is an orexigenic neuropeptide produced by adipose tissue, capable of inducing a significant increase in peripheral blood lymphocytes as well as the percentage of cytotoxic lymphocytes in mice. It is a sensor of negative energy balance, reduced during obesity and increased by energy restriction. This hormone also regulates immune function by reducing pro-inflammatory cytokines and promoting thymopoiesis during ageing[27,28].

Obese patients, particularly those with visceral fat accumulation, have reduced plasma levels of adiponectin, the most abundant and adipose-specific adipocytokine. Evidence suggests that adiponectin has anti-atherogenic, anti-inflammatory and anti-diabetic properties, because low levels of adiponectin in obesity promote T lymphocyte chemotaxis[29,30].

On the other hand, recent research has shown that the gut microbiota may be regulating obesity by increasing energy uptake and storage from the diet, modifying peripheral metabolism and synthesising gut peptides that control energy homeostasis. These changes in the flora may be caused either by diet, by the use of antibiotics or even by the intake of probiotics[31–34].

The obesity epidemic has promoted the evaluation of all kinds of diets with combination of energy intake and macronutrient content for weight reduction. These diets or regimes may modify gut metabolism including the immune system, through specific effects of nutrients on the gut mucosa or by altering the environment of the microbiota.

Exercise and the immune system

Physical activity is any bodily movement produced by skeletal muscles that results in energy expenditure, i.e. activities that are beyond an individual's daily routine of sitting, standing and walking up stairs. Exercise has been defined as a subset of physical activity that is planned, structured, repetitive and with the objective of improving or maintaining health[35]. It is also important to consider the dose, which is the total amount of energy expended, whereas intensity is the rate of energy expenditure. Thus, physical activity is classified as sedentary, moderate or vigorous and its effects depend on the total amount of time spent in each type[36]. Exercise can also be classified as acute, which refers to a single bout of high-intensity exercise, or as chronic, meaning regular training or practice of a moderate-intensity exercise. Both types of exercise have different metabolic effects; in the case of insulin resistance, both are helpful, but through different mechanisms. On the other hand, the effect of acute exercise on immune cell counts is large, but the effects on the cell function are relatively small[37,38].

The most recent worldwide guidelines for the control of overweight and obesity, as well as for the maintenance of health and well-being, include physical activity at various levels of intensity and duration. The direct relationship between diet and physical activity for the control of

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weight has been well established. Any activity additional to the resting metabolic rate will utilize the body's fat stores at certain points, and so an increase in energy expenditure will be useful to maintain body weight or even reduce it. Some exercise researchers even propose that physical activity is more important than dietary modifications[39].

The extensive promotion of physical activity has increased research on its effect on various metabolic systems. The immune system is no exception and a whole research area has emerged as 'exercise immunology'[40].

During acute exercise, blood leucocyte populations, as well as cytokine concentrations, increase, whereas after the exercise, lymphocytes decrease. Neutrophil functions such as adherence, chemotaxis, phagocytosis and oxidative burst increase with moderate exercise. However, chemotaxis and degranulation are reduced with acute exercise. With respect to repetitive bouts of acute exercise, the information is controversial and the effect is apparently related to the intensity of the exercise and the duration of rest between sessions[41]. Exercise training has been demonstrated to improve macrophage function[42].

The regular practice of moderate exercise has been found to enhance vaccination through a better CD4+ T-cell proliferative response in a murine model[43]. It has been suggested that regular exercise induces TNFα suppression due to the production of IL-6 and other anti-inflammatory cytokines when muscle contraction occurs, and this also promotes lypolysis and fat oxidation[44].

With respect to mucosal immunity, most of the research has been done in the respiratory tract mucosa, particularly measuring secretory IgA in saliva. Most researchers conclude that acute and high-intensity chronic exercise causes immunosuppression, decreasing secretory IgA concentrations that might also be related to the increase in respiratory infections immediately after competitions in athletes[45–47].

Information on the effect of physical activity on the gut indicates that acute exercise may cause transient diarrhoea and that continuous moderate exercise may protect against colon cancer, diverticulosis, gastrointestinal haemorrhage and inflammatory bowel; however, the mechanisms for this effect are not well understood[48,49].

Not much information is available at this point on the effect of exercise or physical activity on adipokine secretion and the available information relates mainly to adiponectin than to any other adipokine.

In a Japanese study of obese young female subjects, high levels of leptin and TNFα and lower levels of adiponectin were inverted with the exercise training programme[50]. On the other hand, exercise in children did not show improvements in C-reactive protein, IL-6, TNFα, adiponectin, leptin, or resistin[51]. In a combined protocol of diet and exercise in men, only diet had a significant positive effect on adiponectin, due to a reduction in fat mass[52]. Adiponectin levels showed an improvement in obese adolescent girls only with a combination of exercise and diet[53].

There is much evidence indicating that recommended (between 30 and 60 min/d) levels of exercise improve systemic immune response. However, there is not much information on its effects on gut mucosal immunity, although it most probably exerts an important benefit.

Combined effects of diet and exercise on the immune system

A study of obese men with or without metabolic syndrome, who were placed on a high-fibre, low-fat diet with daily aerobic exercise, showed improvement in traditional metabolic syndrome markers, but more importantly, a reduction in inflammation, leucocyte–endothelial interactions, adhesion and monocyte chemotactic activity, as well as leucocyte production of matrix metalloproteinase-9, independent of weight loss[54].

Apparently exercise is capable of inducing IL-6 gene expression in adipose tissue as well as in muscle, thus enhancing fat metabolism and increasing the need of NEFA post-exercise, and this effect was significantly reduced by the intake of carbohydrates[55]. It has also been shown that the exercise-induced increase in leucocytes, neutrophils and monocytes may be decreased by carbohydrate intake, as well as the production of C-reactive protein, cortisol and IL-6[56].

On the other hand, supplementation with fish-oil (*n*-3 fatty acids) together with moderate exercise apparently does not modify neutrophil chemotaxis or adherence, nor cytokine production by T-cells or monocytes, but does reduce reactive oxygen species production by neutrophils[57]. A study of various levels of dietary fat intake showed that maintaining an adequate percentage of fat in the diet helps control the exercise-induced inflammatory state in healthy subjects[58].

A mouse model with voluntary exercise or dietary modification showed that energy restriction enhanced natural killer cell function and reduced mitogen-induced T-cell proliferation, whereas exercise had the opposite effect, increasing T-cell proliferation and cytokine production from Peyer's patches[59].

In a study where rats were placed on a high-fat or soyabean-supplemented diet with or without exercise (swimming), spleen T-cytotoxic (CD8+) cells were higher in the soyabean group and interferon-γ was increased with the soyabean and exercise group[60].

In order to evaluate the effect of moderate exercise on gut mucosal immunity, we have done experiments on Balb/c mice with high fat or high carbohydrate diets, with 20 min swimming sessions on 5 d per week, starting at weaning (21 d) up to 12 weeks of life. Partial preliminary results (Fig. 1) on cell phenotype of Peyer's patches show that the fat diet with exercise increases total T-cell percentage, due to an increase in CD3+/CD8+ cells. With respect to B-cells, we observed a decrease in the exercise groups (II Aranda-González, BE Martínez-Carrillo, RA Jarillo-Luna and R Valdés-Ramos, unpublished results).

Conclusions

It is clear that most of the research undertaken to identify the relationship between physical activity and diet with the immune system has focused on the systemic effects and

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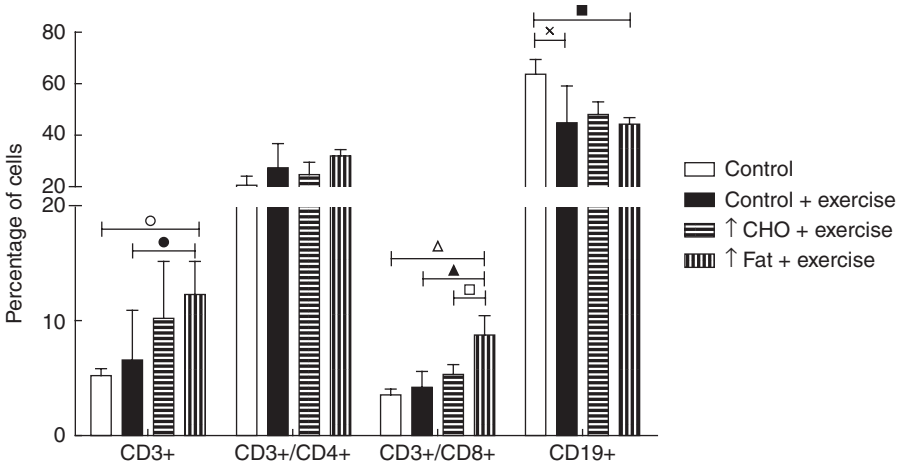

Fig. 1. Peyer's patches lymphocyte sub-populations by flow cytometry. Values represent mean (SD) of each experimental group (*n* 6). Statistical differences by ANOVA with post-test Tukey comparing all four groups, significance for selected columns is as follows: ○, $P = 0{\cdot}023$; ●, $P = 0{\cdot}038$; △, $P = 0{\cdot}0001$; ▲$P = 0{\cdot}0001$; □, $P = 0{\cdot}002$; ■, $P = 0{\cdot}036$; ×, $P = 0{\cdot}007$.

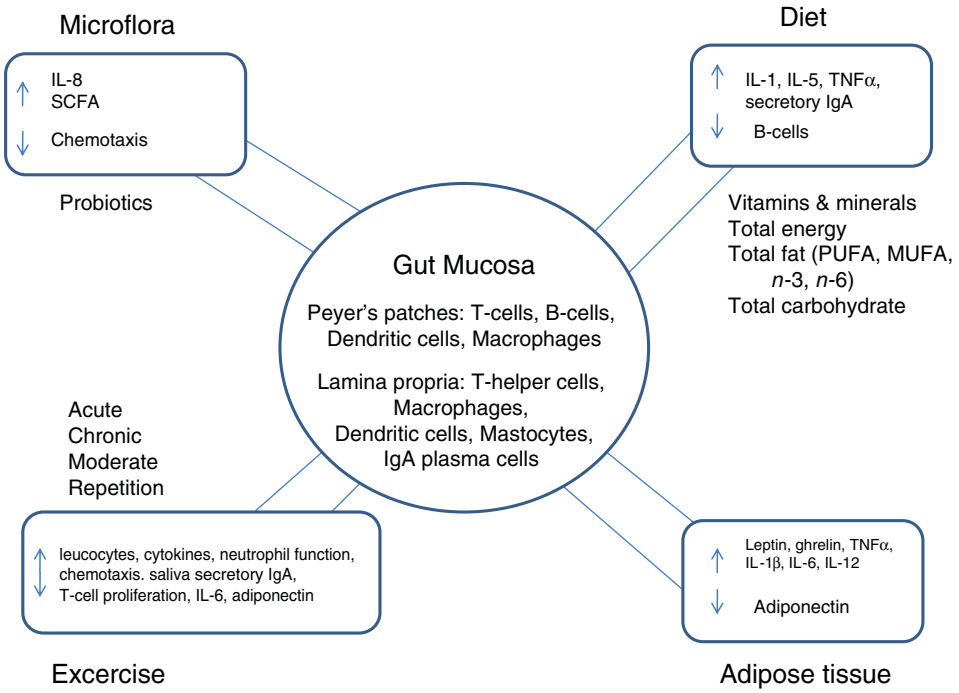

Fig. 2. Factors affecting the gut mucosal immune system. Dietary components affect cytokine secretion; changes in adipose tissue as well as different types of exercise exert modulating effects on cytokine and adipokine secretion as well as specific cellular functions; microflora may also be acting on some components of the immune system and the intake of probiotics may be acting to maintain the balance at this level.

particularly on the inflammatory processes associated with the obesity epidemic and its co-morbidities. However, since the gut is the point of entry of all nutrients and a great amount of antigens, and is the home of a great number of beneficial bacteria, we consider that it is very important to study the direct changes on the gut mucosal immunity caused by all the novel interventions for the control of obesity, CVD, diabetes mellitus and hypertension among others. Research on the gut mucosa of human beings is not an easy task, and so we have developed an animal model that is helpful in learning how these interventions act directly on the local immune system and subsequently on the whole organism.

Exercise modifies the immune system depending on the type, duration and intensity, as well as dietary modifications in the form of total energy restriction, variation in

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the macronutrient content or the intake of probiotic foods that may reinstate the adequate balance of the gut microbiota. Combined interventions of all three components might also be helpful in the control of this worldwide epidemic. There is still much research to be done in order to find the best combination.

Figure 2 summarizes the possible relationships that may be acting on the well-being of the gut mucosal immunity.

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