Chapter 10
Pets and Immunomodulation

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Abstract The immune system is fundamental for survival. Its development and functions are modulated by various genetic and environmental factors. Pets are an important environmental factor, and pet ownership may have relevant immunomodulatory effects. Pets may induce immune modulation via changes induced in gut, cutaneous and respiratory microbiome in pet owners. Such immunomodulation-associated changes may have positive health outcomes. In fact, these may include a contribution towards reducing the risk of developing allergic diseases, if exposure to pets begins in early infancy. In addition, pet ownership may also have other beneficial health effects, namely, reduced psychological stress and depression, which, in turn, may be associated with positive immunomodulatory effects. Finally, pets may also stimulate their owners to have higher levels of regular physical activity and exercise, activities that also have potentially positive effects upon various functions of their owners' immune system.

Keywords Pets · Pet owners · Immune system · Immune modulation · Microbiome · Allergies · Stress · Depression · Physical activity

10.1 Introductory Note

It is generally accepted that keeping pets may have a positive influence upon health-related parameters. However, little is known regarding the effects pet ownership may have on the immune system. The objective of the current chapter is to attempt

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M. R. Pastorinho, A. C. A. Sousa (eds.), *Pets as Sentinels, Forecasters and Promoters of Human Health*, https://doi.org/10.1007/978-3-030-30734-9_10

to clarify these aspects. However, before we can delve into what is known about possible pet-associated modulation of the immune system of pet owners, we first have to briefly analyse the principal features of how the human immune system works.

10.2 General Operational Features of the Human Immune System

The immune system is a complex network of cells and mediators that interact in order to perform an essential function: to discriminate between "self" (molecular sequences which are part of the organism) and "non-self" ("extraneous or foreign") molecules, in various settings (Burnet 1940; Billingham et al. 1956; Janeway 1992; Matzinger 1994).

The capacity which allows the immune system to mount an adequate response, in situations it identifies as those that involve "non-self" molecular sequences or "danger signals", is absolutely crucial. It distinguishes the immune system from all other body systems and makes it indispensable for survival, as demonstrated in HIV^+ patients with severe decreases in the numbers and function of $CD4^+$ T lymphocytes, who succumb to overwhelming infections and various forms of neoplasia. However, the immune system, as happens with all biological systems, is under complex functional control. This type of control is important and is certainly involved in an amazing property of the immune system: the capacity to adapt its responses to different substances it contacts with. This capacity is based upon two features that are crucial to a robust and adequate response: the specificity of the response and the capacity to generate immunological "memory". Thus, globally, the immune system has to perform a very complex and tailored balance between two principal objectives. The first one is to adequately respond to "non-self" molecular sequences that the body contacts with (microorganisms, certain chemical agents, etc.) or "danger signals/alarmins" released by trauma-, viral- or tumour-affected body cells; in this case, the immune system builds responses which lead to the elimination of those molecular sequences (Kang et al. 2015; Nie et al. 2016). The second objective is, in contrast, to develop responses that lead to immunological tolerance. Such tolerance applies to various "non-self" molecular sequences, namely, those that belong to certain microorganisms belonging to gut or respiratory microbiota or foods that are ingested. Such tolerance aims to avoid hypersensitivity reactions and promote tolerance to "self" molecular sequences, thereby averting inappropriate, deleterious responses against cells and mediators of the body the immune system belongs to and which might lead to situations of pathological autoimmunity and autoimmune diseases (Zharkova et al. 2017).

Thus the molecular ability for discrimination is the basis of the mechanisms carried out by the immune system, which contribute towards body homeostasis. However, it is necessary to artificially break down the immune system into two

components, in order to better understand how it operates. These two components are the innate and the acquired or adaptive branches of the immune system. Although they have their own mechanisms, it is important to acknowledge that these two branches work in collaboration.

The innate branch of the immune system includes a diverse array of cells and mediators, which constitute a first line of response against external ("non-self") agents or atypically expressed internal ("self") agents. In operational terms, innate immune responses are triggered by recognition of anomalous expression of "self" or "non-self" antigens, acting as a first line of response, and the mechanics of their action does not involve memory, significant specificity or significant improvement between the first and subsequent contacts with the same antigens. Apart from physical and chemical barriers, the innate immune system involves the actions of cells such as monocytes/macrophages, dendritic cells, natural killer (NK) cells, innate lymphoid cells (ILC), basophils, eosinophils and neutrophils, in various combinations (Mitchell and Isberg 2017).

In contrast to innate immunity, the adaptive or acquired branch of the immune system developed later in ontogenic evolution and is found only in vertebrates. It involves cells such as T lymphocytes (also known as T cells) and B lymphocytes (also known as B cells), as well as mediators known as immunoglobulins (antibodies of various isotypes: IgM, IgG, IgA, IgD and IgE). In particular, it is the adaptive immune system which ensures the previously mentioned essential features of specificity, adaptiveness, discrimination between "self" and "non-self", and memory (Chaplin 2010; den Haan et al. 2014; Pradeu and Du Pasquier 2018).

T cells, in particular, are absolutely essential to the induction and modulation of immune responses, namely, in terms of their specificity and memory (Chaplin 2010; Singh et al. 2017). In the body, they recirculate along various routes (tissues, lymph, blood), which allows them to take on a crucial role in immune surveillance against infectious microorganisms or tumour cells. These are the "effector" T cells, which can be globally subdivided into $CD4^+$ T cells and $CD8^+$ T cells. In addition, some T lymphocyte subsets have regulatory functions ("regulatory" T cells or Tregs) which they exert upon effector T cells in order to avoid excessive responses, namely, against self-antigens so that pathological autoimmune situations can be averted, or against external, non-self-antigens, with a view to avoiding excessive, hypersensitivity reactions, such as those that involve allergies (Sakaguchi et al. 2006; Mohr et al. 2018).

$CD8^+$ T cells essentially act through mechanisms involving direct cytolysis of target cells, whereas $CD4^+$ T cells preferentially operate via cytokine synthesis which allows them to stimulate and optimise functions of other cells they interact with, namely, macrophages and B cells (Chaplin 2010; Schmidt and Varga 2018). The interaction between T lymphocytes and other cells of the immune system is of paramount importance to the development and functions of not only the latter but also the former. In fact, in order to be fully functional, T lymphocytes need cells to present them stimulating peptide fragments (antigens), inserted into MHC (major histocompatibility complex) molecules expressed on the cell membrane of the antigen-presenting cell (Bustos-Morán et al. 2016). Cells with such a capacity are,

in fact, known as antigen-presenting cells (APC) and include macrophages, dendritic cells and B cells. On the other hand, once activated by antigen presentation, T cells also stimulate and improve the functions of APC. In this context, T cells induce macrophages and dendritic cells to become better at engulfing microorganisms and presenting antigens derived from them. In addition T cells also optimise antibody production by B cells and help them to become either full antibody-producing plasma cells or quiescent "memory" B cells, which are necessary for triggering adequate responses on a second contact with the same antigens (Ise 2016).

In practical terms, albeit in an incomplete fashion, immune responses can be broken down into two essential subtypes: those against "external" antigens and those against "internal" antigens.

10.2.1 Responses to "External" Antigens

If pathogenic bacteria enter the human body, the immune system can detect these bacterial cells as sources of foreign/"external" ("non-self") antigens since they express molecular patterns (pathogen-associated molecular patterns – PAMPs) that are not usually present in humans. Innate immune system cells that detect these foreign cells are usually resident in tissues and include APC such as macrophages and dendritic cells. For recognition of PAMPs, these cells use various families of receptors, broadly known as PRR (pathogen recognition receptors), among which Toll-like receptors (TLR) feature prominently. Recognition of PAMPs via PRR activates macrophages and dendritic cells, leading to the release of pro-inflammatory mediators such as prostaglandins, leukotrienes, bradykinin and other mediators (Rosenblat et al. 2014; Tartey and Takeuchi 2017). These molecules trigger a local inflammatory response which also includes the release of pro-inflammatory cytokines. These include IL-1β, IL-6 and tumour necrosis factor-alpha (TNF-α) which are released by dendritic cells and macrophages (Hodes et al. 2015; Rosenblat et al. 2014), thereby leading to the recruitment of immature monocytes as well as neutrophils from the blood into tissues where bacteria are present. Recruited monocytes can further differentiate into phagocytic macrophages to enhance inflammatory processes or promote resolution of inflammation (Ginhoux and Jung 2014; Shi and Pamer 2011). Apart from becoming activated due to the PAMP-PRR interaction, macrophages and dendritic cells, as well as incoming neutrophils, also use TLR and other membrane receptors to engulf the bacteria, through a process called phagocytosis, and also have internal microbicidal mechanisms that allow them, in most cases, to destroy these microorganisms. As a result of this process, bacterial-derived peptides are generated within macrophages and dendritic cells and are inserted into MHC molecules which are then expressed on the membrane of these APC. Since the expressed antigens are "external" (in this case, they stem from the engulfed bacteria), they are complexed together with MHC class II molecules, in the so-called endocytic pathway of antigen presentation (Blum et al. 2013). The involved APC then travel, via lymph, to the draining lymph nodes or, via blood, to the spleen,

where they show the membrane-located molecular complex of MHC class II $^{+}$ bacterial peptide/antigen to $CD4^{+}$ T cells. Those $CD4^{+}$ T cells that can specifically recognise this complex become activated and start producing a balanced set of cytokines (Th0-type cytokine pattern: IFN- γ, TNF-α, IL-2, IL-4 and IL-5, among others) which act upon the APC (Touzot et al. 2014). IFN- γ, for instance, can optimise phagocytic, microbicidal and antigen-presenting capacity of macrophages even further. In this context, it should be mentioned that some activated $CD4^{+}$ T cells, when continually activated, may preferentially start producing a biased set of cytokines, essentially involving IL-2 and IFN- γ (known as a Th1-type pattern), rather than a Th0-type (Maggi et al. 1988; Wierenga et al. 1991). In addition, specifically activated $CD4^{+}$ T cells also proliferate, thereby substantially increasing their relative numbers which allows a more robust response. Finally, most $CD4^{+}$ T cells also differentiate into effector T cells, although a small pool will become "memory" T cells, which will become rapidly activated in subsequent encounters with the same bacterial peptides.

Another cell can also present antigens to $CD4^{+}$ T cells: the B cell (Yuseff et al. 2013). In this case, most B cells, which are also located in the draining lymph nodes and in the spleen, can directly recognise bacterial antigens they are specific to and which reach them via the lymph or blood. These bacterial antigen-specific B cells then also act as APC and present these antigens via MHC class II molecules to specific $CD4^{+}$ T cells. Again, these T cells become activated, and both via direct cell-cell contact with the APC B cells and via production of cytokines, these $CD4^{+}$ T cells induce B cell proliferation and optimal production of antibodies against the bacterial peptides. In this context, IFN-γ produced by $CD4^{+}$ T cells interacting with these antigen-presenting B cells helps these B cells to undergo a process called isotype switching. This process allows B cells to stop producing IgM (which is a large molecular pentamer which works better in the blood) and start synthesising other isotypes such as IgG and IgA, which also work very well in mucosal surfaces and other peripheral tissues.

Effector $CD4^{+}$ T cells then exit the lymph nodes and recirculate via lymph and blood into target organs where bacteria are present and where T cells may more efficiently modulate the actions of innate immune cells in order to make them better at eliminating the involved microorganisms (Walling and Kim 2018). By the time these T cells reach the target organ, not only are macrophages and dendritic cells present in the vicinity of the bacteria but also recently migrated neutrophils are locally performing phagocytic activities. Finally, another component of the innate immune system also takes part in the elimination of bacteria: the complement system. Among other actions, the complement system can directly lyse bacteria.

As a result of the actions of the innate and the adaptive branches of the immune system, pathogenic bacteria can be eliminated, and both T and B "memory" cells persist in lymph nodes and/or the spleen, where they will become the source of rapid responses, in case of a future second contact with the same pathogenic bacteria.

The same type of general outline of immune response occurs with external "allergenic" proteins ("allergens"), since these are also taken up by macrophages and dendritic cells, which also present them to antigen-specific $CD4^{+}$ T cells. In

most cases, such antigen presentation leads to balanced cytokine production (a Th0 cytokine pattern, as previously mentioned) (Touzot et al. 2014). However, depending upon various factors, these $CD4^+$ T cells may be driven into producing high amounts of IL-4, IL-13 and IL-5 (known as a Th2-type pattern) (Maggi et al. 1988; Wierenga et al. 1991). These are cytokines that are associated with preferential production of IgE (via the actions of IL-4 and IL-13) and with the influx of eosinophils (due to the actions by IL-5) into peripheral tissues. These are the two main features of allergic responses, and Th2-type $CD4^+$ T cells are crucial determinants of such responses.

Before we move on to responses to "internal" antigens, it is necessary to mention that, in some cases, external antigens can form complexes not with MHC class II molecules but rather with MHC class I molecules. This means that, in this case, the usual endocytic pathway is not used but rather a pathway known as "cross-presentation" (Blum et al. 2013). Specific subsets of dendritic cells are very efficient at using this process, which is quite important to trigger responses to "external" antigens by $CD8^+$ T cells.

10.2.2 Responses to "Internal" Antigens

In contrast to responses generated against "external antigens", those that target "internal" antigens are mainly carried out not by $CD4^+$ T cells but by $CD8^+$ T cells. In this case, peptides are derived from proteins that are located in the cytoplasm of target cells. Responses to virus infection and to tumours are good examples of this type of immune response. When virus-infected cells are activated, they may transcribe and translate viral proteins. Some of these are transported into the proteasome which digests proteins into peptides. These viral peptides are then translocated into the endoplasmic reticulum where they are inserted into MHC class I molecules. Such MHC class I^+ viral peptide complexes are then transported to the cell membrane, where they are expressed (Blum et al. 2013). Circulating $CD8^+$ T cells that specifically recognise these antigens may then become activated, if antigen presentation occurs adequately. Activated $CD8^+$ T cells may subsequently become fully cytolytic and eventually lyse the infected cells which presented viral antigens to them (McBrien et al. 2018). In addition, viral antigen-specific $CD4^+$ T cells may also become activated if APC engulf infected cells which were destroyed by $CD8^+$ T cell-driven cytolysis. Activated $CD4^+$ T cells, which produce high levels of IL-2 (most frequently in a context of a Th1-type cytokine pattern), may also further contribute towards $CD8^+$ T cells becoming cytolytic, since IL-2 is a major inducer of cytolytic features in $CD8^+$ T cells. Again, each time a $CD4^+$ or $CD8^+$ T cell is activated, there is cell proliferation and differentiation with most cells becoming effector T cells and a minor proportion developing into "memory" T cells. Finally, viral antigen-specific B cells may also become activated and produce antibodies against those antigens, under the influence of viral antigen-specific $CD4^+$ T cells.

It is also important to highlight that, in some cases, both viruses and tumours downregulate expression of MHC class I on affected cells. This means that these

cells cannot activate $CD8^+$ T cells (since these cells only respond to MHC class I-mediated antigen presentation by cells) and, therefore, escape immune surveillance. However, one type of cell that belongs to the innate immune system – the natural killer cell (NK cell) – may become activated in this context of absence of expression of MHC class I molecules and lyse these virus-infected or tumour-affected cells (Kumar 2018).

10.2.3 Further Aspects Regarding Tregs

A subset of T cells, known as "regulatory" $CD4^+$ T cells (Tregs), control immune responses at various levels and use various mechanisms, namely, direct cell-cell contact inhibition or cytokine (IL-10 and/or transforming growth factor/TGF-)-driven inhibition. These cells include various subtypes (Mohr et al. 2018). It is currently known that when such cells are decreased in numbers or functionally deficient, various types of diseases may arise, depending upon the context. Examples include the development of Th1 T cell-driven autoimmune diseases or Th2 T cell-induced allergic diseases.

10.2.4 Development and Maturation of the Cells of the Immune System

All cells of the immune system originate in the bone marrow, via a process called haematopoiesis, which allows stem cells to differentiate into monocytes, T lymphocyte precursors, B lymphocytes, innate lymphoid cells, NK cells, eosinophils, basophils and neutrophils. T lymphocyte precursors, however, need to migrate to the thymus, where they mature into T lymphocytes. After leaving the bone marrow, B cells migrate to lymphoid organs such as the lymph nodes, the spleen and the gut-associated lymphoid tissue (GALT). The same happens to T cells, once they exit the thymus. In fact, GALT seems to be an extremely important lymphoid organ for the full development of the immune system (Lamichhane et al. 2014). In this context, immune cell trafficking is essential for immune surveillance and homeostasis (Takeda et al. 2017).

10.2.5 Factors Affecting the Immune System

Various environmental factors may affect the development, maturation or function of the human immune system. Such influences may be analysed independently, but one must not forget that they will most likely exert their modulating effects in clus-

ters of combinations. Since it is not possible to focus on all environmental factors in this chapter, we will essentially discuss pet ownership-associated factors that most likely influence the human immune system. Such influences include (a) exposure to non-pathogenic microorganisms, which may be associated with adequate maturation of the immune system, changes in human gut microbiota and protection against the development of allergies; (b) the psychological aspects of pet keeping, including a role in coping with stress, depression and anxiety; and (c) physical exercise.

10.3 Pet-Associated Factors with Immunomodulatory Capacity

Research involving the immunomodulatory role of keeping pets, particularly furry ones, is scarce. This review therefore concentrates on research that was carried out in the previously mentioned settings of human exposure to microbiomes; psychological stress, depression and anxiety; and physical exercise and then attempts to extrapolate such findings to the context of pet ownership. In addition, this review focuses on studies performed in humans, with just a few additional studies in murine models that may help to better understand immunomodulatory effects of the factors under study.

10.3.1 Exposure to Non-pathogenic Microorganisms, Modulation of Human Gut and Respiratory Microbiota and Risk of Developing Allergic Diseases

10.3.1.1 Gut Microbiota Modulate Immune Responses

The "hygiene hypothesis" applied to immune development and allergic disease by Strachan (Strachan 1989) and its subsequent adaptations and related hypotheses, such as the "microbiota hypothesis" or the "biota alteration or depletion theory" (Parker 2014), suggest that the lower the degree of exposure to microorganisms in childhood (with changes or depletion of biota, in post-industrial societies), the higher the probability of subsequent development of allergic diseases (and autoimmune diseases and even cancer, cardiovascular or neuropsychiatric diseases) (reviewed by Villeneuve et al. 2018).

Human exposure to microorganisms is a natural phenomenon which is fundamental to the colonisation of the gut, the skin and the respiratory mucosa by high amounts of diverse microorganisms that live in symbiosis with the human body – the microbiota (Eckburg et al. 2005). In ontogenic terms, microbiota are essential to the development and maintenance of adequate body homeostasis. In fact, microbiota have many positive effects, namely, the absorption of various nutrients from

foods, the synthesis of certain vitamins (O'Keefe et al. 2009; Scarpellini et al. 2015) or the metabolisation of undigested nutrients to produce short-chain fatty acids with potent anti-proliferative and anti-inflammatory properties (Pryde et al. 2002; West et al. 2014). However, in certain situations, microbiota that have somehow undergone dysbiotic processes may enhance disease pathogenesis via pro-inflammatory mechanisms (reviewed by Greer and O'Keefe 2011; Schippa and Conte 2014; West et al. 2014).

Colonisation of the gut by microbiota begins in early life, at birth (in utero exposure may be pathological), then undergoes various changes during the first year of life and subsequently remains relatively stable (Spor et al. 2011), although it can be modified by diet and some antibiotics (Abraham and Cho 2009; Cresci and Bawden 2015). Factors that contribute towards gut colonisation of the infant include (a) birth via vaginal delivery, which involves exposure to a mixture of gram-negative and gram-positive bacteria, aerobes and anaerobes (Dominguez-Bello et al. 2010; Makino et al. 2013); (b) breastfeeding (Perez et al. 2007), which is rich in prebiotics that promote the growth of intestinal microbes (Newburg and Walker 2007) and which also contains small amounts of *Bifidobacterium* (Martín et al. 2009); (c) diet, in later childhood (De Filippo et al. 2010; Yatsunenko et al. 2012); and (d) various environmental influences, namely, infections, exposure to aeroallergens or exposure to animals (West et al. 2014).

It should be stressed that colonisation of the human gut is not only important to the maintenance of homeostasis in the host but also in the immune system of the latter. In fact, diverse and rich gut microbiota modulate and train the immune system of the host, by contributing to its development and maturation, namely, in GALT (Mosconi et al. 2013; Macpherson and Harris 2004; Baptista et al. 2013; Geuking et al. 2011; Rakoff-Nahoum and Medzhitov 2008; reviewed by Gensollen et al. 2016 and by Zhao and Elson 2018). In particular, a critical time frame seems to exist from birth until the end of the first year. Such period constitutes a true "window of opportunity" for modulating the morphological and functional development of the immune system and, most importantly, for setting up mechanisms related to immune tolerance to gut microbiota (reviewed by Houghteling and Walker 2015), foods and other antigens (Spor et al. 2011). In fact, if colonisation does not occur during this "window of opportunity", problems of immune development in the gut or other secondary lymphoid tissues may be apparent in adults (El Aidy et al. 2013; Bauer et al. 1963; Gordon et al. 1966).

More specifically, gut microbiota influences the relative composition of intestinal mucosal T lymphocyte subsets with distinct effector functions. In this context, gut microbiota contributes to homeostasis by controlling the relative actions of pro-inflammatory Th1-type $CD4^+$ T cells that produce interferon-γ, Th17 cells (which produce pro-inflammatory cytokines IL-17 and IL-22) and some innate lymphoid cells, as well as the anti-inflammatory actions of $CD4^+$ Tregs. Furthermore, different types of bacteria may modulate the differentiation of different types of effector T cells. In the murine model of germ-free mice, which develop in a microbe-free environment, artificial gut colonisation with filamentous bacteria is associated with the preferential development of potentially pro-inflammatory Th17 cells as well as Th1

$CD4^+$ T cells, whereas other bacteria, such as *Clostridi*a or *Bacteroides fragilis*, favour the generation of anti-inflammatory, regulatory $CD4^+$ Tregs, which produce IL-10, inhibit the development of Th17 cells and provide help with gut homeostasis (Atarashi et al. 2011; Sefik et al. 2015), and contribute towards induction of tolerance to food antigens (Gaboriau-Routhiau et al. 2009; Ivanov et al. 2009). Another aspect must also be emphasised: a lack of $CD4^+$ Treg in germ-free mice is also associated with the development of clear Th2-type (rich in IL-4, IL-13 and IL-5) $CD4^+$ T cell effector responses, which are reflected in high serum IgE levels, due to the IgE isotype-switching effects of IL-4 and IL-13 in mucosal B cells. Again, this pattern can be reduced by gut colonisation with various bacterial types during early life (the window opportunity) but not thereafter (Mazmanian et al. 2005; Gaboriai-Routhiau 2009; Klaasen et al. 1993; Cahenzli et al. 2013).

It should be highlighted that microbiota colonisation of the gut of germ-free mice not only affects the T cell component of adaptive immunity but also B cells. In this case, there is an enrichment of the B cell repertoire and increased production of antibodies by B cells, particularly IgA, upon interaction with T cells (West et al. 2014).

A final aspect involves analysing whether optimal interaction between microbiota and the immune system can be protective against disease and also whether situations of dysbiosis may be associated with the development of diseases such as autoimmune diseases, cancer or allergies (reviewed by Greer and O'Keefe 2011; Schippa and Conte 2014). In fact, various studies have shown that children exposed to microbiota-rich environments, such as farms, from an early age, have a decreased risk of development of allergic diseases (Riedler et al. 2001; Schuijs et al. 2015). Curiously, the protective effect of farm and animal-rich environments may also be associated with increased Treg cell activity in the infant. Thus, although it is not firmly proven, one of the plausible explanations for the protective effect of early life farm exposure is the role of microbiota because individuals exposed to a farm environment possess different microbial diversities compared with other lifestyles (Dicksved et al. 2007). Overall, various studies have shown that reduced gut microbiota diversity during infancy is associated with allergic disease later in childhood (Kalliomaki et al. 2001; Penders et al. 2007a; Vael et al. 2011; Vebo et al. 2011; Bisgaard et al. 2011; Nakayama et al. 2011; Abrahamsson et al. 2012).

10.3.1.2 Pet Ownership Is Associated with Increased Diversity of Dust and Human Gut Microbiota

Having pets such as cats and dogs has been shown to make homes of their owners, namely, house dust, richer in bacterial products such as endotoxin and LPS (Heinrich et al. 2001). In fact, the microbiota in dust from households with cats or dogs is significantly richer and more diverse than that found in homes without pets, as shown in several cross-sectional studies (Dunn et al. 2013; Fujimura et al. 2010; Barberán et al. 2015; Dannemiller et al. 2016; Sitarik et al. 2018). As an example, a study of 746 infants from the Canadian Healthy Infant Longitudinal Development

Study (CHILD) cohort, in which over half of studied infants were exposed to at least one furry pet in the prenatal and/or postnatal periods, showed that pet exposure significantly enriched the abundance of *Oscillospira* and/or *Ruminococcus* bacteria (Tun et al. 2017). Curiously, these types of bacteria have been negatively associated with childhood atopy and obesity.

Furthermore, a recent, longitudinal study aimed to investigate whether introducing a dog into the home changes dust microbiota makeup in the home (Sitarik et al. 2018). Dust samples were collected on-site just before dogs moved into the homes as well as 12 months later. Microbiota composition was compared between homes that did and did not adopt a dog. This study clearly showed that the introduction of a dog into a home significantly resulted in establishment of greater microbiota diversity in that indoor environment. Another study examined a small set of house dust samples drawn from a birth cohort and revealed that dust in homes with dogs had higher relative abundance of specific *Treponema*, *Capnocytophata* and *Moraxella* taxa compared with dust from homes without dogs (Fujimura et al. 2010). Additionally, another study also demonstrated in a sample of approximately 1200 homes across the USA that house dust in homes with dogs had higher relative abundances of *Porphyromonas* and *Moraxella* bacteria, compared to house dust in homes without dogs (Barberán et al. 2015). Furthermore, many of the bacteria enriched in dog homes have previously been identified as common members of the canine oral microbiota (*Porphyromonas*, *Fusobacterium*, *Capnocytophaga* and *Moraxella*) (Sturgeon et al. 2013; Oh et al. 2015), as well as the canine gastrointestinal tract microbiota (*Fusobacterium*, *Prevotella* and *Streptococcus*) (Hand et al. 2013; Middelbos et al. 2010).

Since cats and dogs increase the amount and diversity of house dust microbiota, it is expected that ownership of these types of pets may also change the gut microbiota of their owners. In fact, dog owners tend to share many features of their microbiota, namely, bacterial diversity, with that of their dogs (Song et al. 2013). However, such interplay has not always been observed, and some studies have shown that greater microbe diversity in the environment may be associated with reduced diversity of the gut microbiome in humans (Dicksved et al. 2007). Thus, these aspects have to be further studied.

The precise mechanisms by which a child's gut microbiota can be influenced by their home dust and pet-derived microbiota are not specifically known. Additionally, it is not known whether a specific species or a network of species is necessary to impact the immune system's development. It is possible that many different combinations of bacteria in early life could yield better health in the child, but perhaps the optimal combinations depend on what the child has already been exposed to. In some cases, the prevalence or relative abundance of specific organisms has been associated with atopic diseases. For example, early life colonisation by *Clostridium difficile* reportedly increases the risk of childhood wheeze, eczema and asthma, whereas certain *Firmicutes*, *Bacteriodetes*, *Bifidobacterium* and *Lactobacillus* are regarded as protective (Kalliomaki et al. 2001; Bjorksten et al. 2001; Johansson et al. 2011; Murray et al. 2005; Lynch et al. 2014). A study which analysed the influence of pets and older siblings upon the microbiota of younger sibling showed that

these two traditionally protective "hygiene hypothesis" factors exert distinct effects on microbiota diversity (Azad et al. 2013). These results suggest that the "microflora hypothesis" of allergic disease is probably due to multidimensional changes in the composition of microbiota, rather than simplified variations in general microbiota diversity (Johnson and Ownby 2016).

Another important point should also be addressed. It is currently not clear whether gut microbial composition and immune function changes can be induced after the immune system has been educated in early life. This should be studied since elderly people shut up in care homes with little variety in human contact and little exposure to pets have diminished gut microbiota diversity that correlates with poor health outcomes and increased levels of biomarkers of inflammation such as IL-6 (Claessen et al. 2012).

10.3.1.3 Pet Ownership May Decrease the Risk of Developing Allergies

There have been various studies addressing the issue of whether having a dog or a cat at home in early childhood protects against or increases the possibility of developing allergic disease or respiratory symptoms. Most reports, but not all, have shown that children exposed to dogs (and, less significantly, those exposed to cats) since birth had fewer respiratory symptoms or infections (Hatakka et al. 2010 Grüber et al. 2008; Bergroth et al. 2012). These aspects are particularly relevant, since modern infants and children living in developed countries, particularly those who live in cities, tend to live isolated from contact with non-pathogenic, immune system-modifying bacteria, due to very high and stringent hygienic and disinfectant procedures frequently implemented in most homes. Such procedures lead to low environmental microbial load and reduced microbiota diversity. This may lead to less abundant and/or diverse gut and respiratory microbiota in these children. In this context, keeping a pet such as a dog may increase environmental microbiota diversity, as mentioned before. This may lead to exposure to more abundant and diverse microbiota, which tends to be associated with higher diversity in gut and respiratory diversity of microbiota of pet owners.

We should therefore first analyse results in terms of early exposure of children to microbial diversity. In this regard, the "microbiota hypothesis", a variant of the "hygiene hypothesis", states that environmental microbial diversity influences the developmental process of an infant's gut microbiota ecosystem which subsequently, together with exposure to allergens and microbes, influences the child's development of the immune system and lowers the risk of allergies and asthma (Penders et al. 2007a; Johnson and Ownby 2016; Johnson and Ownby 2017; Wegienka et al. 2010). Although one study showed that infants with eczema had higher faecal microbiota diversity than infants without eczema (Nylund et al. 2013) and a couple of other studies have shown no relationship, most studies have demonstrated that a higher level of diversity in gut microbiota tends to protect children from developing allergies, wheezing or asthma (Remes et al. 2001; Hagendorens et al. 2005; Penders et al. 2007a, b; Nermes et al. 2013; Abrahamsson et al. 2014; Sjögren et al. 2009;

Fujimura et al. 2016; Penders et al. 2013). Since being exposed to dogs and cats during infancy may increase a child's microbiome diversity, it is interesting to analyse whether such feature protects against allergic disease. Dogs, for instance, change home dust microbiota by increasing the types and relative abundances of specific genera (Sitarik et al. 2018). In fact work has shown that children with dogs in the home in the first year of life have greater microbial diversity in their stool (Levin et al. 2016).

Apart from pet exposure-associated child microbiome diversity, the overall relationship between being exposed to furry pets during infancy and protection against subsequent development of allergic disease should also be analysed globally. In this context, although results have not always been consistent, most epidemiological studies have shown that children with regular exposure to livestock and/or pets such as dogs in homes in early life have significantly higher home endotoxin levels and fewer cases of subsequently developed allergy and asthma (Hesselman et al. 1999; Litonjua et al. 2002; Burr et al. 1997; Ball et al. 2000; Ownby et al. 2002; Bufford et al. 2008; Pelucchi et al. 2013; Lodrup et al. 2012; Peters et al. 2015; Wegienka et al. 2011; Wegienka et al. 2010). As an example, the West Sweden Asthma Study (WSAS), which was a population-based study of 788 adults, showed that growing up with livestock or furred pets decreased the risk of sensitisation to various pollen aeroallergens (Bjerg et al. 2016). Furthermore, a meta-analysis of all relevant studies published between 1966 and 2008 assessed the real impact of these exposures on paediatric allergic risk (Tse and Horner 2008). This meta-analysis of 27 studies studying associations between pet ownership and the development of allergic manifestations clearly showed that pet ownership during childhood may lead to a 14% decrease in allergic risk, with dog ownership appearing to be more protective than cat ownership.

It is important to stress once again that previous studies, which showed that pet ownership protected against development of allergies, also showed that household pets increased home endotoxin levels. An interesting prospective study involving three European cohorts showed that the levels of exhaled breath nitrogen oxide levels (FeNO, which is an indirect indicator of eosinophil-rich, Th2-type allergic inflammation) were significantly lower in those children who had had higher endotoxin levels at an early phase of their lives (Casas et al. 2013). In addition, a meta-analysis showed that the risk of allergic manifestations was moderately but significantly reduced in children living in homes with higher endotoxin levels (Tse and Horner 2008). Furthermore, a study performed in the USA showed that the median levels of endotoxin were almost sevenfold higher in Amish rural homes involved in traditional animal-supported farming than in Hutterite rural homes using modern mechanised farming methods, and this was associated with less frequent asthma, lower total serum IgE levels, lower levels of allergen-specific IgE against common allergens and lower percentages of circulating eosinophils in Amish children (Stein et al. 2016). Although endotoxin is not the only microbial-derived product that may affect the immune system, it certainly is a very important one, and its effect may be mediated by Toll-like receptor 4 (TLR4) recognition by macrophages

and dendritic cells and subsequent stimulation of adequate immune responses (Horner 2006).

10.3.1.4 Immune Mechanisms Involved in Pet Ownership-Associated Decrease in the Risk of Developing Allergies

Let us stress again that the immune system needs to contact with microbiota in order to fully develop and acquire its adequate effector and homeostatic functions. Thus, having a furry pet at home increases, as mentioned before, the microbial load and diversity in the house dust. Both adults and children inhale and ingest dust (particularly children), which may be a relevant contributory way to enrich human respiratory and gut microbiota. Not only that, but animals also have their own cutaneous, oral, gut and respiratory microbiota, and interaction with pet owners by licking them or touching them may also play a part in making pet and pet owner microbiota becoming similar (Song et al. 2013).

So, why is interaction with pet-derived microbes immunomodulatory? Well, although very few data exist regarding this specific topic in terms of pet ownership, one can extrapolate information from the broad role that microbes play in shaping our immune system. In fact, when bacteria are present in our gut, they are detected by various receptors on macrophages and dendritic cells. These receptors as well as others that are also expressed on these innate immune system cells allow these cells to phagocytose the bacteria and destroy them by various microbicidal mechanisms. As previously mentioned, this allows presentation of bacterial antigens to specific $CD4^+$ T cells, which then become apt effector cells and, via production of IL-2 and IFN- γ (a controlled Th1-type cytokine pattern), allow macrophages to become even more efficient cells at engulfing and destroying bacteria as well as at presenting bacterial peptide via MHC class II to $CD4^+$ T cells. In addition, IFN- γ induces isotype switching from IgM to IgG in B cells that also present bacterial peptides to $CD4^+$ T cells. This change in isotype allows B cells to produce IgG antibodies that, unlike IgM, can very easily migrate into peripheral tissues in order to exert their functions. It is thus possible that exposure to a farming and animal-rich environment during pregnancy and early infancy modulates Th1-/Th2-type immune responses, as well as Treg responses, and thereby protects against subsequent development of respiratory diseases, namely, asthma in a mother's offspring (Schaub et al. 2009). In fact such an effect may be associated with the induction and maintenance of Th1-type T cell responses (Simpson 2010), rather than allergy-inducing Th2-type mechanisms against environmental antigens. A prospective cohort study involving 239 2-year-old children living in a rural environment in the USA, who had been followed up from birth, indeed showed that the percentage of peripheral blood Th2 cytokine-producing $CD4^+$ T cells was significantly higher in children with doctor-diagnosed asthma and children with wheezing at 2 years of age (Duramad et al. 2006). However, a multiple linear regression model showed that pet ownership and exclusive breastfeeding at 1 month were significantly associated with 35.3% and 34.5% increases in Th1 cytokine-producing $CD4^+$ T cells, respectively. Another, small, study compared production of IFN-γ by mitogen-activated mononuclear cells

from cord blood (CBMC – involving lymphocytes and monocytes) as well as from peripheral blood (PBMC) mononuclear cells, both at birth and at 3 months of age between children born on a farm and those who had not been born on a farm (Roponen et al. 2005). Although there were no differences in IFN-γ production at birth, at 3 months of age, mononuclear cells from children exposed to cats or dogs at home showed an enhanced IFN-γ response. Thus, accepting that there may be a pet-associated decrease in Th2-type $CD4^+$ T cell responses, one may expect levels of IgE to be lower in children who were exposed to pets in their early life. One large birth cohort study from the USA indeed showed that the presence of pets (either dogs or cats) in the home during pregnancy was associated with a lower mean cord IgE level at birth (Aichbhaumik et al. 2008). Similar results were observed in peripheral blood, in a study carried out in 6–7-year-old children who had been exposed to dogs in the first year, and showed that these children had reduced total and allergen-specific IgE levels (Ownby et al. 2002).

Thus, exposure to pets, at least in rural environments, and in infancy, may be associated with a shift from an unbalanced, allergy-associated Th2-type to a preferential Th1-type (or balanced Th2-/Th1-type) of $CD4^+$ T cell cytokine production. This is quite important also because induction and maintenance of Th1-type T cell responses inhibits the development of Th2-type (IL-4-, IL-13- and IL-5-rich responses) T cell responses, which are associated with allergic responses. Thus, exposure to bacteria at an early stage in life (possibly, to a lesser degree, even later on) may help to develop adequate responses against external ("non-self") and even internal ("self") antigens. As previously mentioned, early life exposure to diverse microbiota also allows the development of Tregs. This is most important since various types of $CD4^+$ (and $CD8^+$) Tregs (as well as regulatory B cells) may be crucial in avoiding exaggerated, hypersensitivity-type responses against external aeroallergens (Th2-type responses in allergies) and also exaggerated $CD4^+$ Th1-type and $CD8^+$ cytolytic responses against cells expressing "self" autoantigens (autoimmune diseases). In this context, a study in 285 infants showed that exposure to dogs at home was associated with higher levels of IL-10 (and IL-13) production by mitogen-stimulated PBMC from 1-year-old infants as well as with reduced allergen sensitisation (Gern et al. 2004). This suggests that a more "tolerogenic" profile, possibly due to Tregs, which produce high levels of IL-10, may be induced by regular early life exposure to pets.

10.4 Psychological Stress and the Immune System

10.4.1 Effects of Psychological Stress upon the Immune System

The effects of psychological stress upon immunity depend upon the intensity and duration of its causing agent (Padgett and Glaser 2003; Sorrells and Sapolsky 2007; Morey et al. 2015).

Acute stress is associated with the release of various "stress hormones and mediators", namely, adrenaline and noradrenaline, as well as cortisol, into the bloodstream, with rapid preparation of the body for "fight or flight" reactions. It should be borne in mind that various cells of the immune system express membrane receptors for these "stress hormones and mediators", which allows these haematopoietic cells to respond adequately to such stimuli. In practice, this is reflected in mobilisation of various cells of the immune system (e.g. neutrophils, monocytes, lymphocytes), in the blood, in order to optimise eventual responses to injury or infection (Segerstrom and Miller 2004; Dhabhar et al. 2012). In addition, this is also associated with activation of these cells, with production of pro-inflammatory cytokines, such as IL-6 and IL-1β, whose levels also increase in peripheral blood (reviewed in a meta-analysis by Steptoe et al. 2007). In fact, T lymphocytes may even change their responsiveness to those stress-related neurotransmitters and hormones in order to respond more robustly and rapidly to agents inducing acute stress (Rohleder 2012).

However, if stress becomes chronic, immunological responses become strained, and features associated with immune dysregulation may arise, namely, in terms of cell trafficking and activation in peripheral blood and various organs (McEwen 2012). Chronic stress is associated with the development of two detrimental features in the immune system. These features are, on the one hand, chronic inflammation, which involves higher levels of pro-inflammatory cytokines (Gouin et al. 2012), and, on the other hand, suppression of the innate and the adaptive branches of the immune system, at least in part, due to persistently elevated levels of glucocorticoids (Kiecolt-Glaser et al. 1991; Segerstrom and Miller 2004; Sorrells and Sapolsky 2007). Furthermore, these concurrent features are even more apparent in elderly individuals (Vitlic et al. 2014). Thus, chronic stress-associated systemic inflammation is a form of dysregulation of the immune system which increases the risk of development of chronic inflammatory diseases (Ershler 1993), cancer or autoimmune diseases, as well as the possibility of activation of latent viruses and subsequent infections (Pawelec et al. 2005; Cohen 2005).

In terms of the adaptive immune system, chronic stress may be associated with changes in cytokine production in T lymphocytes. Animal models have shown that such cytokine change involves a shift from a Th1-type to a Th2-type cytokine pattern. As mentioned previously, Th1-type cytokine production (high in IL-2 and IFN-γ) is very important in driving immune responses against both extracellular bacteria and virus infections, as well as against tumours. Thus, stress-induced suppression of Th1 cytokines may decrease responses against many kinds of infections and tumours. Furthermore, since Th1 and Th2 cytokine patterns inhibit each other, stress-associated inhibition of Th1-type T cell responses may lead to activation of Th2 cytokine production, which is a pattern involved in allergies (Marshall et al. 1998). Finally, chronic stress-associated immune dysregulation may also involve a decrease in the number of circulating T lymphocytes, as well as decreased proliferative responses to mitogen responses, both in mice (Dominguez-Gerpe and Rey-Mendéz 2001; Moroda et al. 1997) and in men (Kiecolt-Glaser et al. 1991), as well as changes in patterns of cytokine production, which may increase the possibility of development of autoimmune diseases (Stojanovich and Marisavljevich 2008).

10.4.2 Interaction with Pets May Lower Chronic Stress Levels

Pet ownership may have some beneficial effects in terms of reducing chronic psychological stress. Anti-stress effects of human-animal interactions have been reviewed by Beetz et al. (2012). Various studies have shown that interaction with friendly pets, particularly dogs, is associated with a reduction of stress-related hormonal responses, with a trend towards normalisation of peripheral blood levels of cortisol, adrenaline and noradrenaline. In one study in healthcare professionals, the effects of 20 minutes of quiet rest were compared with 5 and 20 min of interaction with a therapy dog. A significant reduction of reported stress, in association with lower serum and salivary cortisol levels, was found when these professionals interacted with the dogs (Barker et al. 2005), thereby suggesting that cortisol-related immune suppression might be reduced. Similar results showing reductions in plasma cortisol levels were also reported in other studies when adult dog owners were petting their own or an unfamiliar dog but not while quietly reading a book (Odendaal 2000; Odendaal and Meintjes 2003).

Similar results were found in children. One study analysed cortisol levels in children with autistic-spectrum disorder, and related stress, before and after the introduction of a dog into their homes as well as after the dog was removed for a short period of time (Viau et al. 2010). Although no changes in mean diurnal cortisol levels were seen with the introduction or removal of the dog, the magnitude of increase in cortisol levels after waking up (cortisol awakening response) dropped significantly in the morning when the dog was present in the family and increased again upon removal of the dog, thereby suggesting that the presence of the dog normalised the increment in morning peaks in cortisol levels. Another study compared the effect of the presence of a dog with that of a friendly human as social support during a social stress test, on the cortisol levels of children with insecure attachment representations (Beetz et al. 2011). Curiously, the presence of the friendly dog during the test was associated with significantly lower cortisol levels in the children than those observed when there was a friendly human during the test.

All of the above studies show that pet ownership may help to reduce chronic stress, and this may be associated with a decrease in corticoid levels, thereby suggesting that the immune system of pet owners may be less chronically inhibited and/or dysregulated by endogenous corticosteroids. This may, in fact, be suggested by a report which showed a significant increase in salivary immunoglobulin A (IgA) in psychologically stressed college students, after stroking a live dog in comparison with stroking a stuffed dog or sitting quietly for a while (Charnetski et al. 2004). This suggests that pet-associated reduction of psychological stress may contribute towards improved B cell function, as reflected in increased levels of antibody production, although this warrants further research since another study detected no differences between pet owners and non-pet owners before and after interaction with a dog (Krause-Parello et al. 2012).

However, apart from this report, there are hardly any other studies analysing the effects of pet-associated psychological stress reduction on human immunological function.

10.5 Depression, Anxiety and the Immune System

10.5.1 Effects of Depression and Anxiety upon the Immune System

Various clinical and epidemiological studies have shown that depression (and depression-associated psychological stress) is associated with effects on immune function in human adults (Musselman et al. 1998; Padget and Glaser 2003).

Just as happens with chronic psychological stress, these immunological changes are complex and may depend on the severity and chronicity of depression. Nevertheless, changes may involve both a pro-inflammatory component and functional deficits in innate and adaptive immune cells, as is also observed in patients with chronic stress. One meta-analysis showed that peripheral blood levels of the pro-inflammatory cytokines IL-6 and TNF-α were elevated in subjects with major depressive disorder compared with normal controls, thereby suggesting the presence of an inflammatory component in depression (Dowlati, et al. 2010). Another meta-analysis showed that additional immunological factors may also be altered in depression, pointing towards inflammation and cell-mediated immune activation features (Maes 2011). In this context, depression seems to be accompanied by indicators of activation of cellular immunity, namely, increased serum levels of the soluble IL-2 receptor (sIL-2R), as well as increased numbers and percentages of $CD25^+$ ($IL\text{-}2R^+$)-activated T cells. However, the same meta-analysis also showed the presence of glucocorticoid resistance in immune cells, which may contribute to a dysregulation involving inflammation but also immunodepression. In fact, other studies have suggested that depression may, in fact, suppress immune activation. Such suppression may involve reductions in T cell proliferative responses to mitogens and T cell responses to infectious agents, as well as decreases in NK cell activity (Irwin 2002; Irwin et al. 2011; Ford et al. 2018; Kronfol 1983). Furthermore, several meta-analyses, although essentially based on cross-sectional studies (Herbert and Cohen 1993; Weisse 1992; Zorrilla et al. 2001), have shown that depressive disorders are indeed associated with decreased numbers and function of NK cells and poorer T cell proliferative responses to mitogens. This was further shown in a prospective, 1-year-long follow-up study which demonstrated, in a group of 105 healthy individuals, that development of depression was associated with decreased numbers of peripheral blood NK cells (Nakata et al. 2011).

B cell function may also be affected in chronic depression, at least in terms of antibody production. A study performed in measles-vaccinated individuals showed that adolescent and adult individuals with current major depressive disorder had

significantly lower levels of anti-measles IgG antibodies which made them less likely to test seropositive for measles than normal controls (Ford et al. 2018). Thus, this study showed that individuals with major depression were at greater risk of measles infection and severity possibly due to impaired maintenance of vaccine-related protection from measles. Similar results were observed in elderly individuals, in a study which showed that *Varicella zoster* virus (VZV)-specific cell-mediated immunity and VZV-specific $CD4^+$ T cells were significantly lower in the depressed group than in the controls (Irwin et al. 2011). Furthermore, there was a trend for depressive symptom severity to be associated with lower production of IFN-γ.

Various related studies assessed various aspects of immune function in 101 hip fracture patients 6 weeks and 6 months after injury and in 43 healthy age-matched controls (Duggal et al. 2013, 2014a). Thirty-eight of the hip fracture group patients were found to be depressed. There was a significant reduction of superoxide production in response to *Escherichia coli* in the monocytes of these depressed patients compared with nondepressed hip fracture patients or healthy controls. Thus, depressive symptoms may be associated with impaired function, reflected in reduced microbicidal mechanisms in monocytes and neutrophils.

Other studies by the same group, using a similar sample of patients, showed that depressed patients had altered T cell phenotypes, with an increase in activated, senescent $CD4^+$ and $CD8^+$ T cells and augmented production of pro-inflammatory cytokines (TNF-α) (Duggal et al. 2014b). Finally, the frequency of regulatory T cells ($CD4^+$ $CD25^+$ $Foxp3^+$ Tregs) and IL-10 production by $CD4^+$ T cells with regulatory properties and the frequency and IL-10 production by regulatory B cells (Bregs) were also studied in a similar sample of hip fracture patients and healthy age-matched controls (Duggal et al. 2016). A significant reduction in the frequency of Bregs was observed in patients who developed depression compared with nondepressed patients or healthy controls. Bregs also showed a significant decline in IL-10 production in depressed hip fracture patients compared with controls and nondepressed patients. In contrast, there was an increase in IL-10 production by $CD4^+$ T cells in hip fracture patients with new-onset depression compared to hip fracture patients without depression and healthy controls. This study suggests that patients with new-onset depression may have heightened Treg function, with inhibition of various immune functions by these cells, which may contribute to reduced microbicidal function observed in monocytes and neutrophils in these patients.

Interestingly, immune dysregulation in depressed patients may also affect relative expression of Th1/Th2 cytokine patterns in T lymphocytes. In this context, a study showed that parent-reported perceived stress and depressive symptoms in their children were associated with increased levels of the T helper cell type 2 (Th2) markers IL-4 and eosinophilic cationic protein in the latter (Wolf et al. 2008).

Overall, the apparently contradictory findings between inflammation and cellular immune activation and immune depression may have to do with the different study populations and levels of depression in the studied patients. Nevertheless, it is clear that depression changes various functional aspects of the immune system, and such changes may explain the observed higher frequency of infections, autoimmune diseases and cancer in chronically depressed patients.

10.5.2 Pet Ownership May Decrease Depression and Anxiety Levels

Pet owners may be less likely to suffer depression episodes, although the magnitude of this effect clearly varies depending upon the type and age of the animal, as well as the age and health status of the owner.

In a study which analysed depression levels in elderly adults who had been admitted to a rehabilitation unit, those that had been allocated a companion bird during their stay at the ward showed a decrease in depression levels (Jenssen et al. 1996). Another study, carried out in adult psychiatric patients, which compared 15 minutes of reading with 15 minutes of interactions with animals before applying a stressor agent showed that interaction with the animals significantly reduced anxiety levels (Barker et al. 2003). Another study, again in adult psychiatric patients also showed that a 12-week interaction with farm animals was associated with lower state anxiety at 6-month follow-up in the intervention group (Berget and Braastad 2011). Similar results were seen in adults hospitalised with heart failure (Cole 2007). In this study, one group of patients received a 12-minute visit from a volunteer with a therapy dog, whereas another group received a 12-minute visit by a volunteer and the control group just received usual care. When compared with controls, the group who had been visited by the volunteer and therapy dog had significantly greater decreases in anxiety levels, systolic pulmonary artery pressure and pulmonary capillary wedge pressure during and after the intervention. These changes were also associated with significantly greater decreases in epinephrine and in norepinephrine levels during and after the intervention. Thus, this study showed that dog-assisted therapy may decrease anxiety levels and improves cardiopulmonary pressures and neurohormone levels in patients hospitalised with heart failure.

Hardly any studies have addressed the issue of whether pet ownership improves immunological parameters in depressed patients. However, just as occurred with stress, pets also improve depressive symptoms, and this may be associated with improved immune function, although studies are clearly needed to ascertain this.

10.6 Physical Activity and the Immune System

10.6.1 Regular Physical Activity Can Boost the Immune System

Various studies have shown that regular physical activity and exercise training may reduce the risk of diseases such as hypertension and other cardiovascular diseases (Mora et al. 2007; Szostak and Laurant 2011; Ekblom-Bak et al. 2014) or type 2 diabetes and metabolic syndrome (Gaesser 2007; Fleg et al. 2015; Shephard and Balady 1999). In addition, higher levels of physical activity and regular exercise are

associated with reduced risks of all-cause mortality (Blair et al. 1995; Zhao et al. 2015).

In general, regular, moderately intense physical exercise has been shown to have antioxidant and anti-inflammatory action in various tissues, by modulating the ratio between anti-inflammatory and pro-inflammatory cytokine profiles, as well as by interfering with the antioxidant/pro-oxidant enzyme balance (reviewed by Sallam and Laher 2016). Overall, such actions underlie the most frequently observed anti-inflammatory effects of regular physical activity training (Nimmo et al. 2013). Furthermore, regular physical exercise also stimulates functions of the immune system (Turner and Brum 2017). However, one should be aware that the type and intensity of physical activity performed clearly influence inflammatory or immunological outcomes. In this context, low-intensity physical activities such as quiet walking or household tasks may not be sufficient to significantly decrease inflammatory parameters. But even so, low-intensity but regular physical exercise may still have a positive effect on the immune system. In a study involving 17 sedentary individuals who started an 8-week-long low-intensity exercise programme, chronic exercise was associated with upregulation of M2 macrophage response markers (CD14 and mannose receptor), which are activated by Th2-type responses, and downregulation of M1 macrophage markers (MCP-1), which are active in response to infections or tissue injury (Yakeu et al. 2010). The relevance of these changes needs to be ascertained. However, quite interestingly, low-intensity chronic exercise was also associated with the development of an anti-inflammatory profile, with an increase in plasma concentration of anti-inflammatory cytokines such as IL-10 and a decrease in IL-6 and TNF-α levels after exercise (Yakeu et al. 2010). Finally, regular physical exercise of moderate intensity has been shown to optimise NK cell numbers and function (reviewed by Bigley and Simpson 2015).

In contrast, evidence demonstrating that regular physical activity of moderate intensity has an anti-inflammatory potential is more robust (Nimmo et al. 2013; Sallam and Laher 2016). In addition, immunostimulatory effects may also be more pronounced. Furthermore, regular physical exercise may also reduce the relative proportion of pro-inflammatory macrophages (reviewed by Walsh et al. 2011), as well as the rate of T cell immunosenescence in elderly individuals (reviewed by Turner and Brum 2017), even though not all studies have shown that regular exercise can affect T or B cell function. A possible, practical reflection of such an effect can be observed in various cross-sectional as well as in randomised controlled studies which demonstrated that regular physical activity of moderate intensity can result in stimulation of higher levels of antibody responses to vaccination, particularly in elderly but also in non-elderly adults (Kohut et al. 2002; Schuler et al. 2003; Smith et al. 2004; Keylock et al. 2007).

Curiously, recent studies suggest that regular physical exercise may increase human gut microbiota volume and diversity (Clarke et al. 2014; reviewed by Monda et al. 2017). All these effects are beneficial for the host, improving one's health status, namely, in terms of homeostasis (Bermon et al. 2015).

10.6.2 Regular Pet-Associated Physical Exercise May Boost the Immune System

Having certain types of pets at home, such as dogs, may drive owners to be physically more active. In fact, dogs need to be walked and enjoy being involved in physical games outside. In some cases, dog owners only marginally, but significantly, walk longer per week than non-dog owners (Bauman et al. 2001). However, most studies addressing this issue have shown that dog owners are more likely to be physically active compared with non-owners (Anderson et al. 1992; Dembicki and Anderson 1996; Bauman et al. 2001; Parslow and Jorm 2003; Thorpe et al. 2006; Cutt et al. 2008; Shibata et al. 2012), although dog ownership on its own does not necessarily imply that dogs are walked by their owners.

Regular dog walking has been shown to be associated with positive health effects, namely, in terms of dyslipidaemia (Dembicki and Anderson 1996) or control of glycaemia in type 2 diabetes mellitus (Peel et al. 2010). However, there appear to be no studies in the literature that have addressed the benefits of pet walking on the immune system. Thus, one has to postulate that if pet owners perform regular physical exercise of the correct intensity (e.g. daily walking the dog), they may achieve some beneficial effects upon the immune system that have been previously described in non-pet owners who exercise regularly. However, such a possibility needs to be confirmed by adequately designed studies.

10.7 Conclusions

Pet ownership, particularly dogs (with which evidence is more robust), may have relevant immunomodulatory effects with associated positive health outcomes (summarised in Table 10.1). Immune modulation may be due to pet-induced changes in gut, cutaneous and respiratory microbiome. These changes may even contribute towards reducing the risk of developing allergic diseases, if exposure to pets started during infancy. In addition, pet ownership may also have other effects which involve reduced psychological stress and depression as well as increased levels of regular physical activity and exercise. Potentially, these effects may also modulate the immune system of pet owners. However, overall, very few or no studies have focused on such relationships and clearly further studies are warranted. In the meantime, I am very glad that I have a dog at home.

Acknowledgements I would like to thank Professor Maria Vaz Patto, MD, PhD, for her kind patience and helpful assistance.

Table 10.1 Synopsis of pet ownership-associated actual and potential modulatory effects upon owners' immune system

		Innate immune system		Adaptive immune system	
	General immunological features	Monocytes/macrophages	Other cells	T lymphocytes	B lymphocytes
Exposure to pet-derived microbiota	Adequate development of gut-related immune system[a] Avoidance of immune dysregulation[a]	Adequate development of gut-related macrophage role in antigen presentation[a]	Adequate development of neutrophil microbicidal roles[a]	Decrease in bias towards Th2-type T cell responses (IL-4; IL-5) Increased Th1-type T cell responses (IFN-γ) Increase in regulatory $CD4^+$ T cells (Tregs)[a] Decrease in pro-inflammatory $CD4^+$ Th17 cells in gut?[a]	Decreased production of total and allergen-specific IgE levels Enrichment of B cell repertoire[a] Adequate production of IgA and IgG antibodies[a]
Psychological stress	Decrease in chronic inflammation[a] Decrease in dysregulation of immune system[a]	Normalisation of impaired microbicidal mechanisms[a]	Normalisation in NK cell functions[a] Normalisation of peripheral blood NK cell numbers[a] Normalisation of impaired microbicidal mechanisms in neutrophils[a]	Decrease in bias towards Th2-type T cell responses (IL-4; IL-5)[a] Increased Th1-type T cell responses (IFN- γ)[a] Normalisation of T cell mitogen-driven proliferative responses[a]	Adequate production of IgA and IgG antibodies[a]

(continued)

Table 10.1 (continued)

		Innate immune system		Adaptive immune system	
	General immunological features	Monocytes/macrophages	Other cells	T lymphocytes	B lymphocytes
Depression and anxiety	Decrease in chronic inflammation (IL-6, TNF-α)[a] Decrease in dysregulation of immune system[a]	Normalisation of impaired microbicidal mechanisms[a]	Normalisation in NK cell functions[a] Normalisation of peripheral blood NK cell numbers[a] Normalisation of impaired microbicidal mechanisms in neutrophils[a]	Decrease in non-specific $CD4^+$ and $CD8^+$ T cell activation[a] Normalisation of antigen-driven T cell proliferative responses[a] Decrease in T cell immune senescence[a] Decrease in bias towards a Th2-type T cell profile[a] Normalisation of $CD4^+$ Treg activity[a]	Increase in numbers and function of Bregs[a]
Physical exercise	Decrease in chronic inflammation (IL-6, TNF-α)[a] Increase in human gut microbiota volume and diversity[a]	Changes in inflammatory / non-inflammatory macrophage balance[a]	Optimisation of NK cell numbers and function[a]	Increase in $CD4^+$ Treg activity (increase in IL-10 production)[a] Decrease in T cell immune senescence[a]	Normalisation of antibody response to vaccination (particularly in elderly patients)[a]

[a]No pet-related studies have been reported. Results are extrapolated from other studies in humans

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