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19

A Possible Link Between Autoimmunity and Cancer

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1. Introduction

The most important cause of mortality after cardiovascular diseases is due to cancer, that affects both young and elderly people. The increasing incidence of tumour discovery is a consequence of improving diagnosis techniques and sensitization acts, thus facilitating a precocious identification and consequently an immediate therapeutic approach (Malaguarnera et al., 2010).

Autoimmune diseases represent one of the main growing health problem worldwide with wide variations in incidence and severity (Silink, 2002). Autoimmune diseases arise from an overactive immune response of the body against substances and tissues normally present in the body and they are due to the breakdown of immune tolerance to specific self-antigens.

Cancers and autoimmunity are often coincident—more coincident than is generally appreciated; thereby it has been raised more interest the relationship and the possible temporal consequence between autoimmune disease and cancer onset. Particularly, since a high level of autoimmunity is unhealthy, a low level of autoimmunity may actually be beneficial, thereby autoimmune reactions may be considered as a defence processes played by the host against tumour, or it may be possible that the anti-tumour immune response may result in elicitation of auto-antibodies against various auto-antigens, including self antigens expressed in tumour cells.

Some autoimmune diseases, such as Sjögren's syndrome, rheumatoid arthritis and systemic lupus erythematosus have been associated with the development of lymphoproliferative malignancies (Kiss et al., 2010), and a pleyade of autoantibodies have been found in patients with solid tumours (Bei et al., 2009). In addition, patients with dermatomyositis have a greater risk of developing solid-organ malignancies than the general population. In these patients, cancer can precede, parallel or follow myositis diagnosis (Zampieri et al., 2010).

The mechanism behind disease etiology remains unknown for most autoimmune diseases. This situation is distinct from cancer where our understanding of how genetic mutations lead to disease, is increasing. These advancements in cancer biology may have provided a very important piece to the autoimmunity puzzle. However, the relationship between cancer and autoimmunity is not well known. Despite minimal supporting evidence, the standard model for explaining this coincidence is that autoimmunity leads to cancer due to the rapid cell division associated with the regeneration of damaged tissues at the site of

inflammation (Coussens & Werb, 2002). The relationship between autoimmunity and cancer was investigated, focusing on implication of immune system, apoptosis and new therapeutic agents for autoimmune diseases.

2. Break tolerance mechanisms in autoimmune diseases

The clinical signs and symptoms of different autoimmune diseases overlap, and individual patients often present with syndromes that combine features of more than one disease. Different autoimmune diseases share some genetic predisposing factors, including human leukocyte antigen (HLA) alleles (SLEGEN et al., 2008) or the T-cell regulatory gene CTLA-4 (Ueda et al., 2003). Our current knowledge suggests that multiple mutation might be needed before a self-reactive clone bypasses sequential tolerance-checkpoints and gives rise to an autoimmune disease (Baechler et al., 2003). The development of autoantibodies reflects a loss of B- and T- cell tolerance, which might result from a combination of genetic predisposition, persistent inflammatory responses, abnormal handling of apoptotic material and immune complexes, abnormal presentation of self-antigens and other events. As a high level of autoimmunity is unhealthy, a low level of autoimmunity may actually be beneficial. First, low-level autoimmunity might aid in the recognition of neoplastic cells by $CD8^+$ T cells, and thus reducing the incidence of cancer. Second, autoimmunity may have an important role, allowing a rapid immune response in the early stages of an infection when the availability of foreign antigens limits the response (i.e., when there are few pathogens present).

Diseases such as rheumatoid arthritis and tireotoxicosis are associated with the loss of immunological tolerance, which is the ability of an individual to ignore self, while reacting to non-self. This breakage leads to the immune system mounting an effective and specific immune response against self determinants. The exact genesis of immunological tolerance is still unclear, but several theories have been proposed to explain its origin. Two hypotheses have gained widespread attention among immunologists:

- Clonal Deletion theory, proposed by Burnet (1988), according to which self-reactive lymphoid cells are destroyed during their development. The extent to which the thymus can mediate tolerance to tissue-specific proteins and how organ specific tolerance is mediated remains an open question. While some tissue-specific proteins might reach the thymus through the circulation, this mechanism may be unnecessary due to expression within the thymus of the autoimmune regulator protein AIRE, which acts as a promiscuous ubiquitin ligase with the potential function of controlling transcription of a broad array of tissue-specific target genes in thymic epithelial cells (Nagamine et al., 1997).
- Clonal Anergy theory, proposed by Nossal et al. (1982), in which self-reactive T- or B-cells become inactivated in the normal individual and cannot amplify the immune response. This process is based upon the requirement of two signals for T-cell activation. The first is provided by the recognition of MHC-complexes and the second is due to the interaction between CD28 on T cells and B7 on activated antigen presenting cell (APC), that are induced by pro-inflammatory factors, such as bacterial products, pro-inflammatory cytokines, and other signals.

Previously, conditions such as cancer could not stimulate immune responses due to lack of co-stimulatory signals. However, this notion was based on cancers at late or advanced stages of disease, when tumour-induced immunosuppression may be at its highest degree (e.g. through

production of the regulatory cytokines, transforming growth factor (TGF)-β and IL-10); in fact there is a considerable potential for newly transformed cells to evoke danger signals through the engagement of pro-inflammatory signaling pathways (Eisenlohr & Rothstein, 2006).

3. Autoimmune diseases and cancer - pathogenetic aspects

Positive associations have been reported between certain lymphomas and inflammation, autoimmune disease and infectious agents (Rosenquist, 2008).
Normally, tolerance checkpoints silence self-reactive T and B cells by preventing uncontrolled stimulation through self-antigens exposure. Several observations suggest that lymphocyte clones having bypassed tolerance mechanisms may be involved both in autoimmunity and malignancy (Goodnow, 2007). There are epidemiological observations of autoimmunity and lymphoma occurring simultaneously in diseases like systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome regardless of the use of immunosuppressive therapy (Bernatsky et al., 2007).
Infectious agents causing lymphomas can be classified according to several mechanisms. First, some viruses can directly transform lymphocytes as for Burkitt's lymphomas that may occur following infection with HIV; as well as T-cell lymphomas may occur following chronic antigen challenge with wheat in celiac disease (Cellier et al., 2000). Second, some infections increase lymphoma risk through chronic immune stimulation (Engels, 2007), which is also present in autoimmune diseases. Since uncontrolled stimulation of antigen receptors and lymphocyte proliferation triggered by chronic infection (e.g. Helicobacter pylori) may result in mucosa-associated lymphoid- tissue B-cell lymphomas (Suarez et al.,2006), it may be supposed that chronic stimulation of autoreactive cells paired with somatic hypermutation and recombinase activator gene (RAG) activity directed at non-antigen receptor loci may underlie lymphoma in systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome (Schuetz et al., 2010).
Treatments for autoimmune and chronic inflammatory disorders could also affect the risk of lymphoproliferative malignancies. Another reason for the association could be shared environmental risk factors (Landgren et al., 2006), and in some autoimmune diseases genetic mutations are discovered, leading to lymphoproliferation (Turbyville & Rao, 2010). Somatic mutations in lymphocytes may additionally contribute to the pathogenesis of autoimmunity and lymphoid malignancies as observed in patients with autoimmune lymphoproliferative syndrome carrying a mutated FAS gene in a single hematopoietic stem cell that contributes to a small fraction of blood cells. These patients may present with autoimmune symptoms and lymphoma formation just like patients with inherited FAS mutations (Holzelova et al., 2004).

4. The role of adaptive immunity

4.1 Treg cells

Regulatory T (Treg) cells are currently considered as key players in the mechanisms of peripheral immune tolerance. They are classified in natural and inducible $CD4^+CD25^+$ $FOXP3^+$ Treg cells. The transcription regulator FOXP3 (Forkhead box P3) appears to be required for the development, maintenance, and suppressor function of Treg cells (Hori et al., 2003), and the loss of FOXP3 in Treg cells - or its reduced expression - leads to the acquisition of effector T-cell properties including the production of non-Treg cell specific

cytokines (Wan & Flavell, 2007). Treg cells are engaged in the control of immune self-tolerance, allograft rejection, allergy, and are also important for inhibiting the effector functions during infection and tumours development. In addition, the removal or a functional defect of Treg cells from normal rodents leads to the development of various autoimmune diseases (Weiner, 2001), because these cells actively suppress the activation and expansion of autoreactive immune cells.

Sometimes the studies investigating the role of Treg cells in SLE, have given controversial results (Khun et al., 2009). Most studies have found a reduced or normal frequency of Treg cells in SLE (La Cava, 2008), although other studies may have shown increased number. It has been observed a decreased number of Treg cells, during active disease flares (Miyara et al., 2005) and active SLE pediatric patients, thereby showing a poor suppressive capacity and an inverse correlation between Treg cells and disease activity as well as autoantibody levels (Lee et al., 2006). However, treatment with corticosteroids and/or immunosuppressive agents has been found to promote an increase in the number of Treg cells, particularly of peripheral Treg cells. Also, increased mRNA levels of CD25, FOXP3, and GITR have been found in B-cell depleted patients treated with rituximab at the time of B cell repopulation (Cepika et al., 2007).

In the collagen-induced arthritis model of systemic joint inflammation, the adoptive transfer of Treg cells protects from disease, whereas a depletion of Treg cells accelerates it (Morgan et al., 2005). Furthermore, in patients with early rheumatoid arthritis (RA), a reduced number of peripheral Treg cells is observed (Lawson et al., 2006), although the synovial fluid can often contain increased numbers of Treg cells (Cao et al., 2003).

Furthermore, increased frequency of $Foxp3^+$ Treg cells has been documented in tumour tissues and peripheral blood of patients with several types of cancer consistent with a role in tumour escape from immunological control. And also, not only the quantitative aspect of Treg cells, but also their functions are different between tumour patients and healthy control. Treg cells are considered inhibitors of anti-tumour immunity and $CD4^+CD25^+Foxp3^+$ regulatory T cells have been considered as a candidate for cancer immunotherapy for over a decade. Attempts to block or eliminate Treg cells have been made by the use of chemotherapy; these strategies, aimed at block Treg cells induction and migration, may be clinically useful, as suggested by experimental evidences in tumour models (Langier et al., 2010).

Data concerning the role of $CD4^+CD25^+$ regulatory T cells in human cancer derived from a work, which showed that the presence of such Treg cells in advanced ovarian cancer correlated with reduced survival (Curiel et al., 2004). In addition, TGF-β is a cytokine produced by Treg and Type 1 T regulatory cells, that is involved in the suppression of T cell proliferation and function (M.L. Chen et al., 2005). The experimental results supplied by other researchs indicate that TGF-β, secreted by ovarian carcinoma cells, owns vital function in the process of converting peripheral $CD4^+CD25^-$ T cells into $CD4^+CD25^+$ regulatory T cells, likely providing a possible immunotherapeutic target for ovarian cancer (Zheng et al., 2004).

One of the new therapeutic approach to cancer is based on the adoptive transfer of tumour-specific cytotoxic T cells and anti-CD25 antibodies. A combination of Treg cell-depletion, using anti-CD25 monoclonal antibodies, and cytotoxic T lymphocytes administration is a possible approach for treatment of cancers which enable further exploration in the clinical setting (Ohmura et al., 2008), though these future approaches suggest a possible development of autoimmune diseases, due to decreased Treg cells occurrence.

4.2 Dendritic cells

Dendritic cells have been recognized as the most efficient antigen presenting cells that have the capacity to initiate naïve T-cell response *in vitro* and *in vivo*. During their differentiation and maturation pathways, DCs can efficiently capture, process and present antigens for T-cell activation. The functional activities of DCs mainly depend on their state of activation and differentiation: iDC are involved in the maintenance of peripheral tolerance whereas mature DC can efficiently induce the development of effector T cells. Thereby, accumulated iDCs, which are educated at the tumour site, act as functional inhibitors of a tumour-specific immune response in cancer, immature pDCs are activated by Toll-like receptors, which lead to B- and T-cell immune responses in autoimmune disease (Lang et al., 2005). The immunological tolerance is produced by tumour-derived soluble factors (TDSFs) and immature dendritic cells (iDCs), which inhibit DC and T-cell activation, and exclusively inhibit the DNA–IgG immune complex, inducing pro-inflammatory responses needed for an immune response. Immunological ignorance is produced by reduced levels of tumour antigens. Dendritic cells not only initiate T-cell responses, but are also involved in silencing T-cell immune response. DC can play a central role in the development of T-cell tolerance, and its maintenance in the periphery is critical for the prevention of autoimmunity.

4.3 T helper 17 cells (Th17)

T helper 17 cells constitute a third subset of T helper cells that are important in the development of autoimmune diseases and in the immune response against infections. These cells are characterized as preferential producers of IL-17A, IL-17F, IL-21, IL-22 and IL-26 in humans. The IL-17 production is required to differentiate Th17 cells, from IFN-γ producing Th1 cells, or IL-4 producing Th2 cells. IL-17 (A and F) induces production of a broad range of pro-inflammatory cytokines and chemokines, including IL-6, colony-stimulating factors, chemokines (CCL2, CCL7, CXCL1, and CCL20), human β-defensin-2 and matrix metalloproteinases (MMP-3 and MMP-13), by a variety of cells (Weaver et al., 2007). Conversely, inhibition of IL-17 signaling leads to impaired host defence against bacterial infection (Ye et al., 2001) and resistance to autoimmune diseases (Yang et al., 2008). IL-17 regulates host defence against infectious organisms through promoting granulopoiesis and neutrophil trafficking (Linden et al., 2005).

Although $FOXP3^+$ Treg cells are critical for control of autoimmunity and inflammation (Sakaguchi, 2004), Th17 cells have been implicated in mediating inflammation and autoimmune diseases (Weaver et al., 2007). It has been shown that the balance between Treg and Th17 cells is a key factor which regulates T-helper cell function relating to the Th1 / Th2 shift in autoimmune disease and graft versus host disease (GVHD) (Afzali et al., 2007). In fact, elevated levels of IL-17 have been associated with inflammatory diseases in humans, including rheumatoid arthritis, scleritis, uveitis, asthma, systemic lupus erythematosus, and allograft rejection (Kolls & Linden, 2004).

However, there are limited information on the balance between Treg and Th17 cells in cancer patients and on the active role played by Th 17 in anti-tumour immunity (Kryczek et al., 2009). The function of IL-17 in tumour immunity is a controversial subject. The effects of IL-17 on tumour development are directly influenced by the existence of an adaptive immune system. In the presence of lymphocytes, IL-17 promotes tumour rejection, whereas in the absence of those, IL-17 favours tumour growth and angiogenesis (Martin-Orozco & Chen Dong, 2009a). By using IL-17-deficient mice in a model of lung melanoma, it has been provided direct evidence for a protective role of IL-17 in anti tumour responses (Martin-

Orozco et al., 2009b). It has also found that Th17 cells provided better protection to tumours than Th1 cells, and this difference was largely due to their unique ability to promote CD8+ T cell priming. In Th17- but not Th1-treated tumour-bearing mice, it has been observed increased numbers of CD8+ T cells in the lung, suggesting that Th17 cells may promote the activation or recruitment of tumour antigen-specific CD8+ T cells (Martin-Orozco et al., 2009 b). There are data supporting the existence of IL17-producing effector CD8+ T cells (Tc17) which are also induced by IL23 and may play a role in cancer development as well as in autoimmunity (Ciric et al., 2009). Thereby, the protective role of Th 17 cells, inhibiting tumour growth, may influence the onset of autoimmune diseases.

5. Apoptosis mechanism

Apoptosis is an active, genetically controlled process of cell death required to ensure that the rate of cell division were balanced by the rate of cell death in multicellular organisms. The control of apoptosis is critical for the homeostasis of the immune system as it happens during infections, where antigen specific lymphocytes need to rapidly proliferate. After clearance of the infectious microbe lymphocytes need to die in order to prevent dysregulated proliferation with the consequence of leukemia or lymphoma (Lorenz et al., 2000). Importantly, as explained below, during apoptotic breakdown many nuclear constituents are post-translation modified, possibly altering antigenicity. Therefore it is not surprising that failure to achieve programmed cell death and to clear apoptotic cell fragments may be discussed as a key pathogenetic factor leading to autoimmunity. This could be explained by a failure to kill an autoreactive cell or by inducing autoantibodies against apoptotically modified cellular constituents. If the preload is excessive, as in massive cell death (e.g. upon infection), regulatory clearance mechanisms cannot effectively remove apoptotic residuals and thereby allowing the persistence of antigens for stimulation of the immune system. During apoptosis, the cellular contents of the nucleus, cytosol and membrane are brought together in close proximity, a mechanism that could lead to epitope spreading (Vidalino et al., 2009). Altered structures of intracellular proteins produced during cleavage events in apoptosis could also be a source of immunogenic antigens. Altered apoptosis mechanism is associated with the pathogenesis of a wide array of diseases: cancer, neurodegeneration, autoimmunity, heart disease and others.

5.1 Phases of apoptotic death

Apoptotic cell death can be divided into a "triggering phase" (e.g., ligation of "dedicated death receptor" such as Fas, or withdrawal of growth/survival factors), a "signaling phase" (e.g., protein kinase cascades that include MAPK family, JNK and p38), an "execution phase" (e.g., activation of caspases and nucleases), and a "burial phase" (e.g. phagocytosis of dying cells by neighboring cells) *(*Utz & Anderson, 1998*)*.

5.1.1 Triggering phase

Fas ligand (FasL) and tumor necrosis factor α (TNF-α) are the prototypical inducers of apoptosis. These ligands induce clustering of their respective receptors (Fas, TNFR-I or TNFR-II), which leads to recruitment of the early signal-transducing molecules. The Fas/FasL system is the most studied receptor mediated apoptotic pathway. Fas/Apo-1/CD95 is a type I trans membrane protein with a cysteine-rich extracellular domain and is a member of the tumor necrosis factor receptor (TNFR) superfamily (Itoh & Nagata, 1993*)*. A

variety of cell types express Fas, but differing between tissues for the expression levels. Its ligand, FasL, is a type II transmembrane protein that can also exist as a soluble factor in a stable trimer configuration (Mountz et al.,1994). On ligation of FasL, Fas trimerizes and recruits an adaptor protein known as Fas-associated protein with death domain (FADD, also called MORT-1) through its intracellular death domain (Chinnaiyan et al., 1995). The cytotoxic signal is further propagated as FADD recruits and interacts with another adapter protein as FADD-like interleukin-1β converting enzyme (FLICE), also known as caspase-8 (Muzio et al., 1997). Formation of the Fas-FADD-FLICE/ caspase-8 complex, known as death-inducing signal complex (DISC), facilitates the autocleavage and activation of caspase- 8 (Kischkel et al., 1995). A protein known as inhibitor of FLICE (I-FLICE) and FLICE-inhibitory protein (FLIP) can prevent the formation of DISC required for further apoptotic signaling (Irmler et al., 1997).

5.1.2 Signaling phase

Apoptosis is a multistep process and protein kinases have been implicated both in the upstream induction phase of apoptosis and in the downstream execution stage, as the direct targets for caspases. The serine/threonine protein kinases that have been suggested to play a role in apoptosis are the mitogen- activated protein kinase (MAPK) family, specifically, p42/ 44 ERK, p38 MAPK and c-Jun N-terminal kinase (JNK), cyclic AMP-dependent protein kinase A (PKA), protein kinase B (PKB), or Akt and protein kinase C (PKC). The activation of JNK/SAPK and p38 MAP kinases is generally associated with the promotion of apoptosis, while p42/44 ERK activity inhibits apoptosis (Mc Cubrey et al., 2000).

5.1.3 Execution phase

In mammalian cells, activation of caspases is achieved through at least two independent mechanisms which are initiated by distinct caspases, but results in activation of common executioner caspases. Once activated, caspase-8 can induce either directly or indirectly the activation of a number of distal caspases such as caspase-3, -6 and -7 (CD95 type I cells) (Muzio et al., 1997). Another pathway for caspase activation involves cytochrome c, which in mammalian cells is often released from the mitochondria into the cytosol during apoptosis (CD95 type II cells) (Scaffidi et al., 1999) (fig.1).

5.2 The cell death regulator: Bcl-2 and TNF-R

The B cell leukemia-2 (Bcl-2) was the first mammalian cell death regulator identified. Bcl-2 and the tumor necrosis factor receptor (TNF-R) family contribute to the regulation of apoptosis with their corresponding ligands. The proto-oncogene Bcl-2 has been cloned from the t(14:18) chromosomal translocation breakpoint in human follicular centre B lymphoma (Korsmeyer, 1995) and its function was first discovered when it was over-expressed in cytokine-dependent haematopoietic cell lines. Upon removal of the growth factor, Bcl-2 promoted survival of these cells in the quiescent state (Gerl & Vaux, 2005). An important discovery from the studies in lymphocytes was that Bcl-2 did not only promote survival of growth factor-deprived cells but could inhibit apoptosis triggered by a broad range of physiological or experimentally applied cytotoxic stimuli (Sentman et al., 1991). Bcl-2 family can be divided into two groups according to their function: those which are structurally most similar to Bcl-2 and inhibit apoptosis, on the other side there are the members of the Bcl-2 family that enhance cell death. The mitochondrial pathway, is triggered by

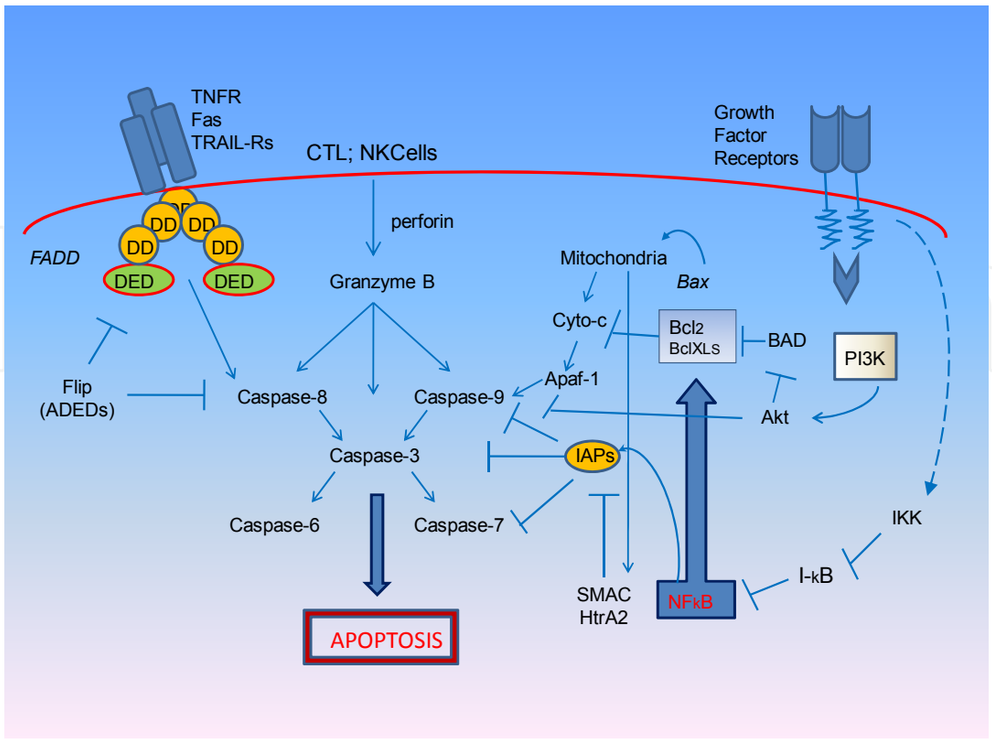

Fig. 1. ADEDs: Anti-apoptotic Death Effector Domain proteins; Akt: serine/threonine protein kinase ; Apaf-1: Apoptotic protease activating factors-1; BAD: Bcl-2-associated death promoter protein; Bax: Bcl-2–associated X protein; Bcl-2: B-cell lymphoma 2; Bcl-xl: B-cell lymphoma-extra large; CTL: Cytolytic T-cells; Cyto-c: Cytochrome-c; DED: Death Effector Domains; FADD: Fas-associated death domain; Flip: FLICE (Fadd-Like Interleukin-1β Converting Enzyme) inhibitory protein; HTRA2/Omi: mammalian homolog of the bacterial high temperature requirement protein (HTRA); IAPs: Inhibitor of apoptosis protein; IKK: IκB kinase ; IκB: Inhibitor of κB ; NFkB: nuclear factor kappa-B; NK: Natural Killer; PI3K: phosphatidylinositol 3-kinase ; SMAC: Second Mitocondrial-derived Activator of Caspase ; TNFR: Tumor Necrosis Factor Receptors; TRAIL-Rs: TNF-related apoptosis inducing ligand-Receptors.

proapoptotic members of the Bcl-2 family. In response to environmental cues these proteins engage another set of proapoptotic Bcl-2 members, the Bax sub family residing on the mitochondrial outer membranes or in the cytosol. The interaction induces the latter to oligomerize and insert into the mitochondrial membrane (Eskes et al., 2000). Here the complex acts to trigger the sudden and complete release of cytochrome c and other proteins from all of the mitochondria in the cell. Bcl-2 block death by preventing the mitochondrial release of the intermembrane proteins, including cytochrome c (Moriishi et al., 1999). A protein with the dual name of Smac/DIABLO is released from the mitochondria along with cytochrome c during apoptosis, and this protein functions to promote caspase activation by associating with the Apaf- 1 apoptosome and inhibiting inhibitor of apoptosis proteins.

Members of the tumour necrosis factor (TNF) receptor family and their corresponding ligands are critical regulators of apoptosis, and also control other cellular processes (Wallach, 1997). CD95 (also called Fas or APO-1) and p55 TNF-RI receptors, and a few other members of the family, contain a cytoplasmic region, called “death domain” (DD), which is

essential for inducing apoptosis (Tartaglia et al., 1993). Upon receptor activation, the death domain undergoes interaction with a death domain in the adaptor proteins FADD (Fas-Associated protein with Death Domain)/Mort-1 or TRADD (Tumor necrosis factor receptor type 1-associated DEATH domain protein) (Hsu et al., 1996). FADD/MORT 1 binds directly to CD95 and indirectly to p55 TNF-R I via TRADD, and it is essential for cell death signaling from both receptors. This complex binds caspase-8, therefore inducing its self-processing (Boldin et al., 1996). The members of the TNF receptor family (death receptors) bearing death domain can also activate signaling pathways that promote survival, proliferation, and differentiation of cells. Signaling via TRADD is essential for TNF-induced activation of Jun kinase and its absence renders cells less susceptible to the pro-apoptotic activity of TNF (Yeh et al., 1997). Death domain RIP (receptor-interacting protein) kinase is required for TNF-receptor transduced activation of NF-kB and its absence also sensitizes cells to TNF-induced apoptosis (Kelliher 1998). This indicates that Jun kinase and NF-kB elicit signals that protect cells against death receptor-induced apoptosis. Moreover, FADD/MORT1, which was originally thought to transducing only a death signal (Hsu et al., 1996), it is now known to be also essential for mitogen-induced proliferation of T lymphocytes (Zhang et al., 1998).

5.3 The role of apoptosis in development, function and homeostasis of lymphocytes

Apoptosis plays a critical role in the immune system, both during the development of B and T cells in primary lymphoid organs as well as during immune responses of mature lymphocytes (Strasser et al., 1995). Programmed cell death is thought to be responsible for the elimination of immature B and T cells that failed to receive a survival signal due to both the lack of growth factors, and either to the failure to productively rearrange antigen receptor genes, or failure of the T cell antigen receptor on thymocytes to bind to MHC molecules on stromal cells (lack of positive selection) (Lu & Osmond, 1997). The effector functions of activated lymphocytes (i.e. secretion of antibodies, production of cytokines or cytotoxicity) are potentially hazardous and it is therefore beneficial to delete these cells when an infection has been overcome (Strasser et al., 1995). The survival of T lymphoblasts is controlled by two distinct mechanisms, both availability of growth factors (e.g. IL-2) and exposure to death ligands (e.g. Fas ligand), which are produced by T cells themselves as a consequence of repeated TCR stimulation (Brunner et al., 1995). The lack of IL-2 triggers a death pathway that can be inhibited by Bcl-2, instead the pathway triggered by Fas ligand is insensitive to Bcl-2 and its homologues (Newton et al., 1998). The death pathway controlled by growth factors and Bcl-2 is thought to be responsible for removing T cells activated by foreign, non-persisting antigens, while death receptor-signaling is critical for removal of activated T cells specific to self-antigens or persistent foreign antigens (Van Parijs et al., 1998).

6. Apoptosis in autoimmune disease

The association between autoimmunity and apoptotic cell death is under extensive investigation. The process of apoptosis defines a series of biochemical and morphologic events that contribute to the normal homeostasis and regulation of immune autoreactivity (Mevorach et al., 1998). During apoptosis, the cellular components as the nucleus, cytosol and, membrane are brought together in close proximity, a mechanism that could lead to epitopes spreading. Altered structures of intracellular proteins produced during cleavage events in apoptosis could also be a source of immunogenic antigens, as cleavage by

granzyme B is a common phenomenon for the release of autoantigens. If cell death is excessive, regulatory clearance mechanisms may not effectively remove apoptotic debris, thereby leading to the persistence of antigens for immune system stimulation. Also, the resistance to clearance by defective proteins may lead to autoimmune phenomenon. Furthermore, the rapid clearance of apoptotic cells by macrophages is important to inhibit inflammation and autoimmune responses against intracellular antigens. Mice deficient in receptor tyrosine kinases, such as Tyro 3, Axl, and Mer, have defective clearance of apoptotic cells, lymphadenopathy, and features of autoimmunity (Scott et al., 2001). A common feature of autoimmune diseases such as systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome, and mixed connective tissue disease is the breakdown of tolerance to self antigens, which induces the production of antibodies reactive with multiple self proteins (Von Muhlen & Tan, 1995). Accumulating evidences show that modifications of autoantigens during apoptosis lead to the development of autoantibodies, thus bypassing normal mechanisms of tolerance (Amoura et al., 1999). Furthermore, direct evidence exists associating faulty apoptotic machinery with the development of autoimmune disease in experimental models and in human disease. Genetic evidences have shown that defects in individual cell-death genes can lead to autoimmune disease. In humans, direct evidence was found in deficient Fas patients, leading to the development of the autoimmune lymphoproliferative syndrome, manifested by lymphadenopathy, renal disease and hemolytic anemia. This syndrome parallels the autoimmune phenomena found in mrl/lpr mice that lack the Fas protein (Straus et al., 1999). In addition, expression of a bcl-2 transgene in mouse B lymphocytes causes extended survival of B lineage cells, sustained humoral immune responses and consequently accumulation of non-transformed B cells and plasma cells and increased levels of serum Ig (O'Reilly et al.,1997). Auto-antibody-secreting plasma cells have been found in normal individuals, but they had no detrimental effect since they were relatively infrequent and short-lived. Expression of a bcl-2 transgene prolongs the survival of such cells and consequently auto-antibodies reach pathogenic levels.

6.1 Apoptosis and systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease clinically characterized by a broad variety of symptoms, mostly affecting the joints. In Europe the incidence of this disease is about 1/10,000. Based on new therapeutic approaches, most of the patients will experience a remission and about 90% of SLE patients are still alive after a five year follow-up (Pons-Estel, et al., 2010). The etiopathogenesis of SLE, although partially understood, is due to multifactorial process. Genetic predisposition in association with environmental factors, including infectious agents, drugs, occupational factors, and food may lead to profound alterations in immune system (Love,1994). These changes include the appearance of autoantibodies with different specificity, altered T cell function, as well as a defective phagocytosis and changes in oncogenes (Kalden et al., 1991). In the pathogenesis of systemic lupus erythematosus an important role is due to a dysregulated apoptosis, which may contribute to development of the disease, regulating the induction of nuclear antibodies frequently found in SLE. This hypothesis is partly based on experiments with an animal model used for SLE (i.e. MRL/lpr mice). Mutational inactivation of the genes encoding CD95 (lpr) or its ligand, Fas ligand (gld), cause lymphadenopathy and SLE-like autoimmune disease in mice (Adachi et al., 1995). Two spontaneous mutations found in the CD95 gene have been considered the cause of deficient expression of a membrane molecule Fas/Apo-1 (CD95). Animals with a deficient expression of Fas/Apo 1 molecule showed an insufficient

elimination of lymphocytes, leading to the assumption that autoreactive lymphocytes could survive and consequently cause autoimmune phenomena (Watson et al., 1992). However, in all humans with SLE the Fas/Apo-1 dependent apoptosis pathway was unaffected (Mysler et al., 1994), and patients with a defect in the Fas/Apo-1 molecule develop a non malignant lymphoproliferation (Rieux-Laucat, 1995). Although this, it has been reported in patients with SLE increased numbers of apoptotic lymphocytes and macrophages (Emlen et al., 1994). Likely, this could be the result of both a fail during the apoptosis phase and an increased triggering of apoptosis, thus delaying the end of programmed cell death process. A sustained apoptotic activity, due to continuous stimuli, is responsible of producing autoantigens, which may lead to the development of autoantibodies directed against macromolecular complex, thereby acting some pathologic effects. In summary, SLE is a complex disorder in which defects in apoptosis and impaired clearance are strong contributing factors for susceptibility, onset and severity of the disease.

6.2 Apoptosis in rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease, characterized by chronic synovial inflammation and synovial cell proliferation, both responsible of "pannus" production. Its development is related to mononuclear cell infiltration, neoangiogenesis, and abnormal proliferation of fibroblast-like synoviocytes (FLS). The pathogenesis of the rheumatoid pannus, has been partly explained by a study on FLS biology (Pap et al., 2000). Two general mechanisms contribute to synovial hyperplasia: increased FLS proliferation and decreased synoviocyte apoptosis. However, apoptotis of synovial cells has been also identified in histologic sections, suggesting that the relative rate of apoptotic cells to proliferating cells is suppressed in proliferating tissues such as in the synovium of RA patients (Sekine et al., 1996). Several studies have examined the mechanisms that could contribute to the resistance against Fas-mediated apoptosis in RA, demonstrating that though Fas is normally expressed by the cells of the pannus both *in vivo* and *in vitro*, the persistence of synovial proliferation in RA patients may lead to bone damage and cartilage erosion (Kawakami et al., 1999). The function of the Fas/FasL system seems to be inadequate to eliminate the cells in the proliferating RA synovium suggesting a strong anti-apoptotic effect in the RA joint.

FLICE inhibitory protein (Flip) is highly expressed at sites of erosion, in the pannus, in the lining, and in the areas of the synovial tissue where apoptosis has not been observed (Perlman et al., 2001). This prospect was supported by the fact that, when synovial tissues were examined by immunohistochemistry, high levels of Flip were associated with low levels of apoptosis in early RA. In contrast, decreased Flip was detected later in the disease course, and this was related with increased apoptosis and decreased numbers of macrophages (Catrina et al., 2002). In addition, it has been supposed that the potential beneficial effects of TNF-α antagonist therapy might be related to the reduction of Flip, which would permit Fas/FasL-mediated apoptosis and result in subsequent clinical improvement.

In the antigen-induced arthritis model of RA, Bcl-2 was present at sites of early erosion and correlated with levels for erosion and inflammation, thus supporting the importance of this factor. Since either the presence of Bcl-2 or anti-apoptotic Bcl-2 family members (Bcl-2, Bcl-xL, A1 and myeloid-cell leukaemia sequence 1) at sites of early erosion in antigen-induced model of arthritis was greatly expressed on synovial fibroblasts, in the synovial lining and in the sublining region from RA patients, it has been largely examined the potential

mechanisms that may contribute to the augmented expression of Bcl-2 (Perlman et al., 2001). Activated NF-kB, has been implicated in the regulation of gene transcription that contributes to cytokine generation, expression of cell surface adhesion epitopes, lymphocyte maturation, protection from TNF-α induced apoptosis, and antigen processing and presentation by MHC class I molecules. NF-kB is expressed in almost all cell types, and plays a significant role in regulating the production of inflammatory cytokines, such as TNF-α, IL-1 and IL-6, as well as anti-apoptotic molecules such as Flip (Pope & Perlman, 2000). Different cytokines such as IL-lβ, platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor β (TGF-β) and TNF-α are present in synovial tissues of RA patients, promoting the proliferation of human synovial cells. Fas antigen expression on synovial cells is inhibited by the addition of TGF-βl with up-regulation of Bcl-2, Bcl-xL and XIAP. The expression of FLIP, is increased in bFGF-treated synovial cells. These results show that bFGF treatment augmented the expression of FLIP, resulting in resistance toward Fas-mediated apoptosis. The tumour suppressor gene p53 regulates cell cycle, DNA repair, and inhibits angiogenesis. Although, early study reported an upregulation of p53 expression in RA joints (Firestein et al., 1996), a more recent interesting study about the role of several genes, involved in apoptosis mechanisms, reported that p53 gene was deeply reduced in peripheral blood mononuclear cells from patients with RA, SLE, insulin-dependent diabetes mellitus and multiple sclerosis compared with that in normal controls; thus suggesting, that the decreased expression of p53, might contribute to the development of autoimmune disease, possibly by failing to eliminate potentially pathogenetic cells (Maas et al., 2002). Its increase is due to DNA damage, thus permitting DNA repair through cell cycle prolongation, or leading to apoptosis in more severe cases. Deletions, mutations or other mechanisms leading to its lost are often associated with tumour growth.

Although Fas and FasL are greatly expressed on synovial lining macrophages, paucity of apoptosis within the joint might be the result of a variety of mechanisms. An improved understanding of the mechanisms regulating apoptosis will provide insights to aid with a more effective therapy patients with RA.

6.3 Apoptosis and Sjögren's syndrome

Sjögren's syndrome (SS) is a chronic autoimmune disorder, occurring primarily in women, affecting the salivary and lacrimal glands. The histopathological changes in the minor salivary gland biopsy are characterized by the infiltration of these glands by mononuclear cells with secondary destruction of the parenchymal tissue, resulting in oral and ocular dryness (Moutsopoulos et al., 1980). The pathogenesis of glandular damage in Sjögren's syndrome is currently poorly understood; however, the predominance among the infiltrating mononuclear cells of activated $CD4^+$ T cells suggests that cell-mediated immunity plays an important role in tissue destruction (Skopouli et al., 1991). In recent years, it has been reported that the expression of the apoptosis regulating-proteins in salivary glands of Sjögren's syndrome patients suggests a role for apoptotic cell death in the pathogenesis of glandular damage (Patel & McHugh, 2000). The resistance of infiltrating mononuclear cells to apoptosis may result in longer survival that might also increase the production of pro-inflammatory cytokines and autoantibodies, or predispose to the late development of lymphoma in some Sjögren's syndrome patients. T lymphocytes induce apoptotic cell death through either the release of proteases, such as perforin and granzymes,

or the interaction of FasL, expressed by activated $CD4^+$ T cells, with Fas on target cells (Russell & Ley, 2002). In murine models, defective signaling and blocked apoptosis caused by mutations in Fas or FasL resulted in autoimmune disease as well as lymphadenopathy (Skarstein et al., 1997). Corresponding mutations were not found in genes encoding Fas and FasL in primary Sjögren's syndrome patients (Bolstad et al., 2000). However, it has been suggested that increased levels of Fas induced apoptosis among epithelial cells explaining the damage of the glands. On the other hand, increased expression of intracellular anti-apoptotic molecules could lead to dysregulation of apoptosis and the formation of large foci of infiltrating mononuclear cells. In the field of autoimmune disease, a common feature is the lack of specific serum markers of disease. Among the most widely used serological markers in confirming the diagnosis of Sjögren's syndrome (SS), there are anti-SSB/La and SSA / Ro antibodies, with a prevalence between 70 and 80% . Although this prevalence is high, they are not specific for Sjögren's syndrome, but also found patients with other autoimmune diseases: anti-SSA / Ro in 35% of patients with systemic lupus erythematosus and 85% of patients with congenital heart block (BCC), and anti-SSB / La in 15% of patients with systemic lupus erythematosus. SSA and SSB are two ribonucleoproteins, located mainly in the nucleus and in the cytoplasm. In patients with Sjögren's syndrome it has been recently studied a new autoantibody that recognizes a structural protein, bound to actin, and that is part of the cytoplasmic skeleton: the α-fodrin (Ulbricht et al., 2003). The fodrin has a localization predominantly near the inner surface of the cell membrane and physiologically it participates in the process of cellular secretion. When antibodies directed against the α-fodrin are present, the cellular mechanism of secretion is impaired. Since the salivary glands are rich in α-fodrin, their secretory mechanism is inhibited, resulting in xerostomia and keratoconjunctivitis sicca. Therefore α-fodrin antibodies would more precocious than those commonly used in the diagnosis of SS (anti-Ro and anti-La), especially in the early stages of the disease. The cleaved α-fodrin fragment has been shown to be a marker of apoptosis (Janicke et al., 1998). Furthermore, a monospecific antibody recognizing the cleaved α-fodrin is available. In Sjögren's syndrome, cleaved α-fodrin autoantigen is greatly expressed on ductal epithelium, on sporadic acinar cells and strongly associated with infiltrating mononuclear cells, however it is rarely detected in normal salivary glands. Further studies are required to verify the specific association of cleaved α-fodrin with primary and secondary Sjögren's syndrome. Therefore based on results of studies of SS-like disease in mice, there may be 2 distinct phases in the pathogenesis of SS (Humphreys-Beher et al., 1999). The first, a lymphocyte-independent step may be characterized by a genetically determined anomaly responsible for epithelial cell apoptosis, resulting in either the production of nucleosomes or the exposure on the cell membrane of autoantigens, such as α-fodrin, SS-A (Ro), and SS-B (La) ribonucleoproteins. In fact, apoptosis allows the translocation either of the ribonucleoproteins SS-A (Ro) and SS-B (La) or the cytoplasmic protein α-fodrin on epithelial cell membranes, where they may be exposed to antigen-presenting cells such as macrophages, and thus generate an autoimmune response (McArthur et al., 2002). After this phase, an elevated expression of proinflammatory cytokines and metalloproteases also may occur, with consequent degradation of epithelial basal membranes (Pérez et al., 2000). The second phase is characterized by mononuclear cells (MNC) infiltration, lymphocyte mediated apoptosis through Fas/FasL interaction, perforin and granzyme B release and production of cytokines

(IFN-γ, TNF-α, and TGF-β1) leading to glandular damage and secretory flow injury (Perez et al., 2000). Improved understanding of the primary cellular events responsible for the glandular damage occurring in SS may allow the discovery of new therapeutic strategies able to interfere with the mediators of apoptosis and thus prevent epithelial cell death and consequent impairment of secretory function.

7. Apoptosis and malignancies

Altered function of apoptosis mechanism occurs frequently in cancers and has been implicated in many events relevant for the pathogenesis and progression of tumours, including cell accumulation caused by failure of programmed cell death (Reed, 1999). Thereby, it may be induce a permissive environment for genetic instability and oncogene activation, promote resistance to immune cell attack, and contribute to resist to the cytotoxic effects of chemotherapy and radiation, allowing tumour cell survival. In the same way, defects in DNA repair and chromosome segregation normally trigger cell suicide as a defence mechanism for eradicating genetically unstable cells. Apoptosis defects permit the survival of the genetically unstable cells, and thus provide opportunities of selection of progressively aggressive clones (Anthoney et al., 1996). In addition, apoptosis defects play a role in tumour resistance to hypoxia, growth factor deprivation, immune surveillance mechanisms, chemotherapy, and radiation (Medh & Thompson, 2000). Tumour immunosuppression that favours tumour progression and metastasis is the consequence of the activation of an immunosuppressive network, mediated by several tumour-derived soluble factors, such as interleukin- 10 (IL-10), transforming growth factor (TGF)- β and vascular endothelial growth factor (VEGF), and which involves the primary tumour site, secondary lymphoid organs and peripheral vessels (Zou, 2005). There are different pathways leading to dysregulated immune responses in cancer and autoimmune disease, such as the impaired clearance of apoptotic cells, played by macrophages. Although the fact that tumour cells generate pro-inflammatory conditions, the immune cells induce an anti-inflammatory environment , due to impaired clearance of apoptotic cells by macrophages during the turnover of tumour cells. The impaired clearance of apoptotic cells induces anti-DNA antibodies to self-antigens that lead to a pseudo-autoimmune status, which, provoking a pro-inflammatory response, allows tumour progression (Kim et al., 2005). The increased concentration of autoantibodies and dendritic cells can induce the production of $CD4^+$ $CD25^+$ regulatory T cells (Tregs) that inhibit T-cell function, causing immunological tolerance (Ward et al., 2004). Thus, it is likely that cancer immunosuppression is produced by tumour-derived soluble factors, due to an anti-inflammatory response to immune cells triggered by a defective apoptotic cell clearance, and increased concentration of Treg cells.

There are significant differences in immunological dysregulation between cancer and autoimmune disease. In the first case, the impaired clearance of apoptotic cells causes accumulation of autoantibodies, which is attributed to the inhibition of T-cell function through increased Treg cells, which play a crucial role in immunological tolerance in cancer cells. In autoimmune diseases, defective apoptotic cell clearance causes accumulation of DNA–IgG immune complexes, which provokes an immune response through Toll-like receptor 9 (TLR9), leading to tissue injury. Unfortunately, the Treg cells are decreased and dysregulated, in this case (Lang et al., 2005).

7.1 Apoptosis and the genes that control it - effect on the malignant phenotype

Elucidation of the genetic alterations of molecules with a central role in apoptosis pathway has provided new insights into tumour biology, revealing novel strategies for combating cancer. More weight has been placed on core apoptosis components such as, Bcl-2 family proteins, death receptor signaling, endogenous inhibitors of caspases, transcriptional control of apoptosis, apoptosis regulation by oncogenes and tumour suppressor genes. The proteins of Bcl-2 family play a key role in the normal regulation of apoptosis and aberrant expression of members of this family has been associated with several tumours. The anti-apoptotic members include Bcl-2 and Bcl-xl and the pro-apoptotic members include Bax, Bad, Bim, Bid (Chang et al., 2003). Experiments involving knockout mice have contributed to our understanding of the role of Bcl-2 family members in tumourigenesis. Bad-knockout mice develop B-cell lymphomas and are less able to hold-out with sub-lethal doses of γ-irradiation (Ranger et al., 2003), while Bid-knockout mice develop myelomonocytic leukemia (Zinkel et al., 2005). Interesting results, involving tumours and Bcl-2, derive from studies undergone on human beings. Over-expression of Bcl-2 has been observed in both B-cell lymphomas (where it was originally discovered) as well as in non-Hodgkin's lymphomas. Furthermore, over-expression of Bcl-2 has been observed in solid tumours such as lung, renal, stomach, and brain cancer. Instead, lower levels of Bcl-2 have been observed in breast cancers. However, either over-expression of Bcl-2 in some subtypes of lymphoma or low levels in breast cancer correlate with poor prognosis (Gascoyne et al., 1997; Chang et al.,2003). It seems that the prognostic value of Bcl-2 expression differs between tumour types and in some cases there may be no correlation with disease progression. The importance of p53 in maintaining genome stability is exemplified by the finding that approximately half of all human tumours carry mutant p53. At present, there are > 10 million people with tumours that contain inactivated p53, while a similar number have tumours in which the p53 pathway is in part blocked by inactivation of other signaling components (Brown et al., 2009). It is well confirmed that the p53 response is defective in most cancers, either by mutations or deletions in the p53 gene, or by alterations in the p53 pathway caused by other oncogenic events. These observations have raised a wide range of clinical possibilities both for diagnosis and treatment, rendering p53 an ideal target for anti-cancer drug design. p53 mutations, the first tumour suppressor gene linked to apoptosis, occur in the most of human tumours and are often associated with advanced tumour stage and poor patient prognosis. Studies using p53 knockout mice demonstrated that endogenous p53 could play a part in apoptosis, in fact p53 has been required for radiation-induced cell death in the thymus, but not cell death induced by glucocorticoids or other apoptotic stimuli (Lowe et al., 1993). p53 can exhibits different and global functions (e.g. promote apoptosis, cell-cycle arrest and senescence). Evidences indicate that p53 apoptotic activity is important in tumour suppression. Therefore, the occurrence of p53 mutations correlates with a decreased apoptosis in some transgenic mice (Attardi & Jacks, 1999) and in clonal progression of tumour cells (Bardeesy et al., 1995). Furthermore alterations of several p53 effectors in apoptosis (e.g. Bax, apaf-1 and casp-9) can promote oncogenic transformation and tumour development in mouse model systems (Soengas et al., 1999). Activation of p53 is sufficient to directly or indirectly trigger apoptosis by inducing pro-apoptotic Bcl-2 family members (Schuler et al., 2000). In addition, alterations in genes encoding various modulators of NF-kB can occur in several types of B-cell malignancies, including non-Hodgkin lymphomas, B-chronic lymphocytic leukemia, and multiple myeloma (Rayet & Gelinas, 1999).

8. The role of TNF-α antagonist therapy in cancer onset

As biologic therapy becomes more common in treating a spectrum of conditions, awareness of side-effects is becoming more important. Mouse models and in vitro experiences indicate that TNF-α plays an important role in tumour growth control. Thus, anti- TNF-α agents might influence the risk of malignancy.

TNF-α is one of main regulator of chronic inflammation and contributes to tumour development, therefore suggesting a role in the progression of solid tumours. However, therapy with TNF-blockers, such as infliximab or etanercept, in patients with advanced cancer was well tolerated, with no evidence of disease acceleration (E.R. Brown et al., 2008). Nevertheless, a systematic review and metanalysis of data from randomized controlled trials of monoclonal antibodies against TNF-α in patients with rheumatoid arthritis showed that there were 29 case of cancers in patients with infliximab group compared to 3 in the control group (Bongartz et al., 2006). In a study of 404 patients with Crohn's disease and 404 matched controls, there were 3 cases of breast cancer in the infliximab-exposed group compared to 1 case in the other group (Biancone et al., 2006). In the Swedish nationwide cancer registry, 4160 patients exposed to TNF-α antagonists (etanercept, infliximab, or adalimumab) were identified (Askling et al., 2005a). Although it has been reported 67 solid cancers, including 8 cases of breast cancer, it has not been found excess risk of solid cancer in this cohort.

TNF-α generates a variety of cellular responses that may either promote or inhibit tumourigenesis. This variability may explain the discrepancies in study results. Some studies on experimental models suggest increased tumour progression with TNF-α blockade. Clinical trials, in contrast, suggest that TNF-α blockade may decrease the activity of solid cancers (kidney and breast). These discordant data generate uncertainty about the potential effects of TNF-α antagonists on the risk of human malignancies in general and on male breast cancer in particular (Williams, 2008). Infliximab is a chimeric mouse-human monoclonal antibody targeting TNF-α. Blocking the actions of tumour necrosis factor-alpha is highly effective in treating several inflammatory disorders. Although safety data have been encouraging, there are reports of immunosuppressive sequelae resulting from the use of the drug.

The soluble dimeric form of p75 TNF receptor, etanercept, binds free TNF in the circulation and cell-bound TNF, thus acting as a competitive inhibitor, blocking TNF interaction with TNF receptors on cell surface (Tsimberidou & Giles, 2002). It inhibits binding of both TNF and lymphotoxin (LT)-a (also known as TNF-β) to cell surface TNF receptors, rendering TNF biologically inactive. It has been postulated that etanercept acts both as a cytokine carrier and TNF antagonist, and can modulate biological responses that are induced or regulated by TNF, such as expression of adhesion molecules responsible for leukocyte migration (Tsimberidou & Giles, 2002). Etanercept has shown activity and is currently indicated in patients with moderately to severely active rheumatoid arthritis; moderately to severely active polyarticular-course juvenile rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs; or psoriatic arthritis (Lovell et al., 2000; Mease et al., 2000). In a pilot study, it was given Etanercept to 13 patients affected by cutaneous T-cell lymphoma (CTCL), because of the role played by TNF in tumour progression. An improvement was observed in patients with early disease, and a larger cohort of patients with early disease merits investigation, while it is unlikely that it will be effective in patients with advanced CTCL (Tsimberidou et al., 2004).

Adalimumab is a fully human recombinant IgG1 monoclonal antibody with specificity for human TNF-α. Bongartz et al. (2006) conducted a systematic review and meta-analysis that included 9 trials employing either infliximab or adalimumab in 3493 patients with RA versus 1512 patients taking placebo to further elucidate the carcinogenic potential of TNF-α blockers. The odds ratio for malignancy was found to be 3.3, and the incidence of cancer was associated with higher doses of the biologic. For patients treated with anti-TNF-α antibodies included in these trials, the number needed to harm was 154 within the 6- to 12-month follow-up period. But the study failed to give some adjustments.

The relationship between lymphoma and TNF-α blockers has been documented in a few case reports focusing on psoriasis patients. One report reviewed relevant data in the MedWatch postmarketing adverse event surveillance system run by the Food and Drug Administration and discovered 26 cases of lymphoma following treatment with either etanercept (18 cases) or infliximab (8 cases) (S.L. Brown, 2002). Frequently, those receiving etanercept were reported to be taking MTX concurrently (5 of 18) or had a history of prior exposure to MTX (4 of 18), or a history of exposure to another immunosuppressive agent (4 of 18). Another noteworthy clinical feature of the lymphomas observed was the very short latent period of only few weeks between the initiation of anti-TNF therapy and the development of malignancy.

In two instances (one etanercept, one infliximab), lymphoma regression was observed following discontinuation of the TNF-α -blocker in the absence of specific cytotoxic therapy directed toward the lymphoma.

The association between lymphoma and biologic therapy was weakened by data reported by Askling et al. (2005b) who epidemiologically studied cohorts of RA patients with either long-standing disease, incident disease, or TNF-α -antagonist treated disease linked with the Swedish Cancer Registry. The lymphoma risk in those treated with TNF-blockers was no higher versus the other RA cohorts, given that the standardized incidence ratio (SIR) for RA patients on TNF blockers was 2.9 and not statistically significant after adjustment for sex, age, and disease duration from the SIR of 2.0 in control subjects with RA.

A study reviewed 1440 patients having psoriasis treated with etanercept for more than 5 years, without founding any increase of malignancies (Burge, 2003). However, a multitude of recent case reports have begun to strengthen the link between anti-TNF-α therapy and induction or rapid reactivation of latent malignancies.

In the literature many case-reports were found about the cancer onset after anti-TNF-α therapy, such as anorectal carcinoma (Melichar et al.,_2006) and non-Hodgkin Lymphoma (Bickston et al., 1999) after infliximab therapy in Crohn's disease, cutaneous and systemic T-cell lymphoma after treatment with infliximab and also with etanercept (Adams et al., 2004).

One reason for the safety concerns surrounding anti-TNF-α therapy is the role of the members of the TNF family in normal immune system development and function (Bazzoni & Beutler, 1996). However, ''knock-out'' mutations of the TNF gene complex in mouse models of disease cause an increased susceptibility to certain infections, but not autoimmunity or malignancy (Erickson et al., 1994). In addition, it is noteworthy the absence of a clear immunosuppressive effects of TNF antagonism in preclinical and human studies. Thus, in contrast to the pleiotropic effects of TNF with the immune system, blockade of TNF with infliximab does not suppress global immune function in the manner of drugs such as azathioprine (Meenan et al., 1997). Therapy with infliximab has not been associated with decreases in absolute lymphocyte counts (Meenan et al., 1997), development of anergy (Feldmann et al., 1997), or emergence of opportunistic viral and fungal infections. Together,

these data suggest that blockade of TNF with a drug such as infliximab may lead to limited and selective rather than broad-spectrum immune suppression.
Also for adalimumab therapy carried on patients affected by rheumatoid arthritis it was observed the incidence of cancer, especially the onset of melanoma in two patients, after two years from the start of therapy with adalimumab (Dewan et al., 2009).
However, it is not easy to establish clearly the real risk associated with anti- TNF-α therapies because of various confounding factors including possible increased predisposition to cancer due to the underlying disorder and the concomitant or prior use of other potentially cancer-promoting therapies.

9. Possible link between autoimmune diseases and cancer

In many systemic autoimmune diseases, where disproportional humoral autoimmune responses are pivotal in the pathogenesis (e.g. systemic lupus erythematosus and Sjögren's syndrome), exaggerated B-cell processes exist, resembling B-cell malignancies (Illes et al., 2009). Both conditions are characterized by cell-cycle regulation abnormalities, which affect lymphocyte survival, proliferation and differentiation, as well.

9.1 Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease, characterized by a wide array of symptoms and organ involvements, leading to varying disease courses and outcome. In patients with SLE, the incidence and risk of malignancy development is increased. The malignancies occurred frequently in SLE patients are Non-Hodgkin's Lymphoma, Hodgkin's Lymphoma, as well as solid tumours, as lung, cervical and breast cancer (Kiss et al., 2010).
The frequent occurrence of malignancies can be associated with the common pathogenetic pathways for cancer and autoimmune disease development. This phenomenon is reinforced by the following notions: generally, in autoimmune diseases malignancies occur with high frequency; in neoplastic disorders, autoimmune diseases can develop, as part of the paraneoplastic syndrome; also, immunosuppressive treatment in autoimmune diseases increases the development of malignancies (Zintzaras et al., 2005).
The long-term, in many instances aggressive immunosuppressive treatment in lupus is evidently related to the development of malignant transformations and manifest tumours. Besides these common extrinsic etiological factors, the intrinsic errors of the immune system contribute to the development of both disease entities (Bernatsky et al., 2002).

9.1.1 Cancer before systemic lupus erythematosus

Since the clinical appearance of Non-Hodgkin's Lymphoma and systemic lupus erythematosus is similar, and it is sometimes difficult to distinguish the two disease entities in the initial phases, these raise the possibility that SLE might be a paraneoplastic syndrome and appears on the grounds of the lymphoid malignancy (Kiss et al., 2010).

9.1.2 Cancer after systemic lupus erythematosus

The pathogenic background behind the more frequent presence of NHL in SLE can be due to the chronic, persistent antigen-stimulus, chronic inflammation, uncontrolled B cell proliferation, defected apoptosis, and the increased risk of oncogene translocation. Common

environmental and genetic factors, linked with major histocompatibility complex (MHC)-associated genes, further contribute to lymphomagenesis in lupus. Also, treatment with immunomodulating and immunosuppressive drugs, commonly used in SLE can contribute to the development of lymphomagenesis, either by directly causing mutagenesis, or by weakening the immune surveillance, which can lead to uncontrolled B cell proliferation (Kiss et al., 2010).

In 9% of SLE patients may occur some inflammatory diseases, such as pneumonitis-fibrosis or bronchiolitis obliterans organizing pneumonia, that may lead to a chronic stimulation and extensive DNA damage which underlie lung cancer.

Moreover, in female affected by SLE it has been reported a higher risk of breast cancer, without any family history or exogenous hormonal exposure (Ramsey-Goldman et al., 1998). Thereby, likely the pathological immune responses triggered by the autoimmune disease can lead to uncontrolled cell proliferation and decreased apoptosis, and breast cancer development, indeed (Kiss et al.,2010).

9.1.3 Antiphospholipid antibodies

Another link between lupus and malignant diseases can be served by antiphospholipid antibodies (aPL), frequently present in SLE and cancer as well.

Patients with cancer are at higher risk of thromboembolic complications than healthy people for many reasons. It is known that an important thrombogenic mechanism is mediated by antiphospholipid antibodies (aPL). Although the evidence on their association, the relationship between aPL presence and cancer is contradictory. It is unclear whether aPL antibody positivity has a pathogenetic role in the development of thromboses or whether, in contrast, these antibodies are an epiphenomenon in cancer patients (Reinstein & Shoenfeld, 2007).

In the last years a higher prevalence of aPL antibodies was observed in patients with solid tumours compared to controls (Zuckerman et al., 1995) and in patients with haematological malignancies (Pusterla et al., 2004). The reasons of this increased antibody production are only partially clarified: their production may be induced by particular immunotherapy of cancer such as interferon α (Becker et al., 1994) or started by immune system response to new tumour antigens (Sawamura et al., 1994).

In particular it is possible that autoantibodies to malignant cells arise secondary to changes in the cell membrane that induce exposure of certain antigens that are normally facing the intracellular compartment (Reinstein & Shoenfeld, 2007), then activating pathogenetic autoreactive human T cells (Yamaguchi et al., 2007). In this context, it has been reported that viable tumour cells (Fernandes et al., 2006) as well as tumour blood vessels (Ran et al., 2002) showed increased exposure of anionic phospholipids on the outer layer of their membranes, directly triggering coagulation cascade by providing a procoagulatory surface (Vogt et al., 1997). Therefore, tumour microenvironment may be a source of anionic lipid surfaces that facilitate aPL antibodies production. It is also possible that tumoural cells directly synthetize antibodies as in the case of multiple myeloma or Waldenstrom's macroglobulinemia (Tincani et al., 2010).

Moreover, an interesting study carried on aPL antibodies healthy carriers, reported that the major cause of morbidity and mortality was the occurrence of malignancies, in particular non-Hodgkin's lymphoma seemed to affect this group with an higher incidence than the general population (Finazzi, 1997).

9.2 Rheumatic arthritis

The link between autoimmune phenomena, particularly rheumatic arthritis, and cancers has been suggested in several studies. It may be due to the generation of autoantibodies against self and non-self antigens, paraneoplastic syndromes or by chemotherapy.

As the presence of autoantibodies has been identified in the sera of patients both with solid tumours and haematological malignancies, it may be considered as the consequence of the immune response against the tumour (Conrad, 2000).

The natural autoantibodies (NAA), frequently occurring in high titres in the sera of patients with multiple myeloma, Waldenstrom's macroglobulinemia, chronic lymphocytic leukaemia, and B cell lymphoma, are generated by CD5+ B cells. They are mainly IgM, which bind with low affinity self and non-self antigens, and they also have rheumatoid factor activity (Abu-Shakra et al., 2001). This autoantibody activity is the result of malignant transformation of B cells, that produce autoantibodies (Dighiero, 1998).

9.2.1 Cancer after rheumatic arthritis

An increased occurrence of malignancies in patients with established rheumatoid arthritis (RA) has been found by several studies (Bernatsky et al., 2006). In most cases, the higher rate of cancer is linked to the use of immunosuppressive therapy, and the tumour generally takes several years to develop.

9.2.2 Cancer before rheumatic arthritis

However, the early manifestation of an occult malignancy may be a rapid-onset arthritis mimicking rheumatoid arthritis. More often, the rheumatoid arthritis-like syndrome precedes the development of cancer by 6–12 months. (Racanelli et al., 2008)

Rheumatoid arthritis-like syndromes have been associated with malignancies of the lung, colon, breast, ovary, stomach and oropharynx cancer and with haematopoietic malignancies. (Andrai et al., 2006)

Patients with paraneoplastic rheumatic disease generally exhibit a form of asymmetric polyarthritis that may be confused with seronegative rheumatoid arthritis or spondyloarthropathy.

The paraneoplastic disorders disappear after surgical removal or pharmacological treatment of the cancer, otherwise these treatments have any influence on rheumatic symptoms that are tumour-associated (Naschitz, 2001).

9.3 Polymyositis and dermatomyositis

The association between malignancy and autoimmune myositis, in particular polymyositis (PM) and dermatomyositis (DM), has been largely described (Briani et al., 2006). The diagnosis of tumour can precede, parallel or follow myositis diagnosis. Most commonly cancer is diagnosed after the onset of myositis, but in many cases the course of the myopathy paralleled the course of the tumour (Zampieri et al., 2010). The incidence of cancer in patients with an established autoimmune myopathies was estimated ranging from 6% to 60% (Hill et al., 2001). In contrast, the incidence of myopathies as an early manifestation of an occult malignancies is undefined.

9.3.1 Cancer before autoimmune myositis

The malignancies more frequently associated with PM and DM are ovarian, colorectal, breast, and lung cancer (Wakata et al., 2002). The so called "paraneoplastic" inflammatory

myopathies are autoimmune myositis, that develop in patients with primary cancer as the consequence of its presence. In the paraneoplastic syndromes the surgical removal or pharmacological treatment of cancer results in the disappearance of the clinical symptoms of the paraneoplastic disease (Raccanelli et al., 2008). Some myopathies can develop also in response to chemotherapeutic agents used to treat cancer (Chakravarty & Genovese, 2003). The paraneoplastic myositis show different clinical features and laboratory data, as well as a later onset and a lower or absent response to immunosuppressive drugs (Buchbinder et al., 2001).

9.3.2 Cancer after autoimmune myositis

Patients with DM have a greater risk of developing malignancy than the general population, while PM patients seem to be associated to a lesser extent to an increased risk. Also the drugs used to treat autoimmune myositis can be responsible for cancer onset in these patients. These drugs are administered in order to modulate the response of immune system and therefore their use can induce an altered state of immune surveillance which can be responsible for the consequent development of tumour (Szekanecz et al., 2006).

The pathogenetic molecular mechanisms underlying the association between cancer and myositis are still unknown, even though some hypotheses have been purposed (Eisenlohr & Rothstein, 2006). It is possible that an immune response directed against cancer cells in both breast and lung adenocarcinoma, as well as hepatocellular carcinoma, cross-reacts with regenerating muscle cells (Casciola-Rosen et al., 2005). These regenerating muscle fibers and tumour cells expressing myositis specific autoantigens, may be responsible for the induction of autoimmune response in those patients with a predisposing genetic background to autoimmunity. Casciola-Rosen et al. (2005) have been demonstrated that some tumours (e.g. breast, lung adenocarcinoma, and hepatocellular carcinoma), but not the corresponding normal tissues, express high levels of myositis autoantigens. It has been also demonstrated that in affected muscles from myositis patients, regenerating myoblasts overexpress myositis specific autoantigens and notably the expression of these autoantigens by tumour cells as well as by regenerating myoblasts, indicates a possible antigenic similarity between the two cell populations (Casciola-Rosen et al., 2005).

9.4 Sjögren's syndrome

The link between Sjögren's syndrome (SS) and non-Hodgkin's lymphoma (NHL) is one of the strongest among all the known associations between systemic autoimmune diseases and malignancies. The occurrence of NHL has been reported to be as much as 44-fold greater in Sjögren's syndrome than in the general population (Kovács et al., 2010). In the majority of patients, the histopathologic type of lymphoma is mucosa-associated lymphoid tissue (MALT) type B cell lymphoma, i.e. extranodal marginal zone B cell lymphoma, and in about 30% of SS patients, other types of NHL can be observed. In SS, the predominant cellular components of the focal lymphocytic infiltration in the salivary glands are CD4+T lymphocytes. The evolution of a malignant proliferation of B-lymphocytes from this inflammatory infiltration is due to a complex process. The ultimate step in this process is the transition from benign B cell proliferation to malignant expansion. The uncontrolled expansion of B-lymphocytes is a result of various genetic alterations, typically translocations involving immunoglobulin gene loci and proto-oncogenes or other genes involved in cell-cycle regulation (Kovács et al., 2010).

10. Conclusion

The relationship between autoimmunity and cancer has been investigated, focusing on implication of immune system, apoptosis and new therapeutic agents for autoimmune diseases. Autoimmune diseases, characterized by chronic inflammatory state, with continuous antigenic stimulation, may contribute to haematological malignancies and solid tumours development. However , the role of new therapeutic agents, as biologic drugs used more frequently in autoimmune diseases treatment, is controversial and need further studies in depth, since they may be involved in cancer onset, as well. The autoimmune diseases, as rheumatoid disorders, systemic lupus erythematosus or myositis may occur before or concomitant with a tumour, as paraneoplastic syndromes, which regress after cancer removal.

Apoptosis is a critical regulator of cellular and humoral immune responses, appearing to play a critical role in the deletion of lymphocytes after an inflammatory state, as well as in the control of tumour cell survival, leading to unchecked tumour growing, if the genes of apoptosis show some mutations. Therefore, understanding normal apoptosis mechanisms is critical for developing a better know-how from which to undertake strategies for improving autoimmune diseases and cancer therapy.

In addition, it is an interesting task the different immune responses against autoantigen occurring during autoimmunity and cancer, which are involved in alterations of immunological tolerance and maintenance of immunological tolerance, respectively. Thus it is easy to understand that immunological tolerance in cancer and autoimmune disease has opposite effects in the patient: in cancer patients it stimulates the growth of the cancer, but in patients with autoimmune disease immunological tolerance may stop the attack by autoantibodies and thereby benefit the patient. In fact, cancer cells are able to employ a pseudo-autoimmune status (cancer associated autoimmune disease) and induce immunological tolerance by producing autoantibodies to tumour antigens derived from impaired clearance of apoptotic cells, resulting in an increase of regulatory T cells, thus increasing tolerance toward tumour cells.

However, further investigations are needed to better define new therapeutic strategies controlling inflammatory components, responsible of both autoimmunity and cancer progression.

11. References

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