Minireview

Pharmacological Modulation of Caspase-8 in Thymus-Related Medical Conditions

Nicola Pozzesi, Alessandra Fierabracci, Trinh Thy Thuy, Maria Paola Martelli, Anna Marina Liberati, Emira Ayroldi, Carlo Riccardi, and Domenico V. Delfino

Foligno Nurse School, Department of Medicine (N.P.), Section of Hematology (M.P.M.), Section of Pharmacology (E.A., C.R., D.V.D.), Department of Medicine, Section of Onco-Hematology, Hospital S. Maria, Terni, Department of Surgery (A.M.L.), University of Perugia, Perugia, Italy; Autoimmunity Laboratory, Immunology and Pharmacotherapy Area, Bambin Gesù Children’s Hospital IRCCS, Rome, Italy (A.F.); and Institute of Chemistry, Vietnam Academy of Science and Technology, Cau Giay, Hanoi, Vietnam (T.T.T.).

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ABSTRACT

The thymus is a lymphoid organ that governs the development of a diverse T-cell repertoire capable of defending against nonself-antigens and avoiding autoimmunity. However, the thymus can also succumb to different diseases. Hypertrophic diseases, such as thymomas, are typically associated with impairment of negative selection, which leads to autoimmune disease, or disruption of positive selection, which results in immunodeficiency. Hypotrophic diseases of the thymus can manifest during acute infections, cancer, allogeneic bone marrow transplantation, or with aging. This condition leads to decreased immune function and can be treated by either replacing lost thymic tissue or by preventing thymic tissue death. Studies have demonstrated the critical role of caspase-8 in regulating apoptosis in the thymus. In this review, we discuss how pharmacological activation and inhibition of caspase-8 can be used to treat hypertrophic and hypotrophic diseases of the thymus, respectively, to improve its function.

Introduction

Thymus Physiology. The thymus is an ancient lymphoid organ that was present in both jawed and jawless vertebrates as a “thymoid” region (Hirano et al., 2013). Composed of thymocytes of hematopoietic origin and thymic epithelial cells (TECs) of nonhematopoietic origin, the thymus is the primary organ responsible for de novo generation of a diverse repertoire of immunocompetent T cells capable of conferring defense against nonself-antigens (Delfino et al., 2011a). T-cell development depends on interactions between antigen major histocompatibility complexes on the surface of medullary TECs and the T-cell receptor (TCR) complex on the surface of thymocytes. In recent years, several novel molecules have been identified as critical modulators of thymic physiology. For example, studies have demonstrated that, in addition to interacting physically with thymocytes, TECs produce soluble factors, such as thymic stromal lymphopoietin. Polymorphisms in the gene encoding this cytokine have been associated with the development of multiple allergic disorders in humans, indicating that thymic stromal lymphopoietin is a critical regulator of T-helper 2-cytokine-associated inflammatory disease (Siracusa et al., 2011).

Other molecules involved in thymocyte differentiation have also been discovered and become the focus of much research. During T-cell development, thymocytes survive by positive selection and are exported to the periphery if their affinity with TECs is weak. One important player in this interaction is Themis, a protein that increases the affinity threshold for activation, thus enabling positive selection of T cells with a naive phenotype in response to low affinity self-antigens (Pu et al., 2017).
CD4+CD8+ SP

- TCR rearrangement
- IGCR1
- cohesin

CD4-CD8- DN

CD4+CD8+ DP

- TSLP
- weak interaction
- TEC

CD4+ or CD8+ SP

- NK-T
- PLP
- positive selection

Thymus Pathology

Impairment of any molecules or processes involved in thymic physiology and thymocyte differentiation can lead to the development of disease. The thymus is the site of proliferative diseases (thymomas) as well as immunodeficiency and autoimmunity. This organ is also affected by extrathymic diseases, such as acute infections, cancers, or allogeneic bone marrow transplantation, all of which provoke thymic atrophy and disrupt the immune response (Fig. 2).

Thymomas are indolent, malignant tumors with a propensity for spreading locally. Thymomas are found in 15% of patients with myasthenia gravis, 50% of those with pure red cell aplasia, and 10% of those with adult-onset hypogammaglobulinemia (Venna et al., 2011; Dettterbeck and Zeeshan, 2013; Seton et al., 2013). Malignant thymomas are also found in 10% of Good syndrome cases (Masuda, 2011). With similar natural killer and B-cell deficiency, one of these cases strongly resembled the phenotype of an Ikaros-null knockout mouse (Ng et al., 2011). A recent report has also demonstrated thymoma development with acquired autoimmune polyglandular syndrome type 1, a monogenic syndrome of pleomorphic autoimmunity characterized by hypoparathyroidism, hypoadrenalism, and candidiasis. Autoimmune polyglandular syndrome type 1 arises from defects in the gene encoding autoimmune regulator, which regulates the expression of tissue-specific self-antigens.

Fig. 1. Thymic microenvironment and T-cell differentiation. The development of thymocytes into mature T cells takes place within the thymus. The three basic steps in this process are: 1) a few CD4+CD8+ double negative cells (orange, left) originating from the bone marrow proliferate and differentiate into CD4+CD8+ double positive (DP) cells inside niches of TECs. During this process, TCR rearrangement takes place through the involvement of intergenic control region 1 and cohesin. 2) The large majority (80%) of DP thymocytes (red, blue, middle) die by neglect (violet) if they do not interact with TECs, while a smaller percentage (5%) die by negative selection as a consequence of an overly strong interaction with TECs (violet). Thymocytes expressing Themis survive by positive selection as a consequence of an appropriately weak interaction with TECs. 3) These thymocytes differentiate into various CD4+SP subsets (natural killer [NK]-T, CD4+, or T regulatory [Treg]) (red) or CD8+SP (blue) cells. The growth factor thymic stromal lymphopoietin (TSLP) produced by TECs is responsible for allergic diseases, whereas the promyelocytic leukemia zinc finger is responsible for NK-T-cell differentiation. IGCR1, intergenic control region 1.
by surface medullary TECs. In the absence of autoimmune regulator, many tissue-specific self-antigens are not expressed in the thymus, resulting in multiorgan autoimmunity owing to faulty negative selection of autoreactive T cells (Cheng et al., 2010).

**Role of Caspase-8 Pathway in Thymic Diseases.** Resistance to chemotherapy is a common challenge with various cancers, and dissecting the mechanisms leading to this resistance can lead to improved therapies. One mechanism of resistance involves the inhibition of caspase-8 (Lee et al., 2012) activation to block apoptosis of cancer cells (Fig. 3). In the example reported in Fig. 3, stimulation of epidermal growth factor receptor blocks caspase-8 activation (Fig. 3, left), whereas inhibition of the same receptor by a chemotherapeutic agent (Fig. 3, right) reactivates the caspase-8 pathway, leading to cancer cell death. The murine thymoma EL-4 cell line is resistant to Fas ligand (FasL)-induced apoptosis because of constitutive expression of the caspase-8 inhibitor c-FLIP. Forced expression of Fas rendered EL-4 cells highly susceptible to FasL-induced cell death, demonstrating that apoptosis is dependent on the expression of c-FLIP relative to cell surface–expressed Fas (Kataoka et al., 2002).

Recent evidence indicates that the long form of c-FLIP (c-FLIP(L)) is required for proliferation and development of effector T cells. c-FLIP(L) transgenic mice exhibit splenomegaly, lymphadenopathy, multiorgan infiltration, high titers of autoantibodies, and proliferative glomerulonephritis with immune complex deposition in a strain-dependent manner. The development of autoimmunity requires CD4+ T cells and may result from impaired thymic selection. At the molecular level, c-FLIP(L) overexpression inhibits ZAP-70 activation and signaling required for thymic selection. Thus, c-FLIP(L) has been identified as a susceptibility factor under the influence of epistatic modifiers in the development of autoimmunity (Qiao et al., 2010).

Ian4, a mitochondrial outer membrane protein with GTP-binding activity, is normally present in thymocytes, T cells, and B cells. A mutation in the rat Ian4 gene results in severe T-cell lymphopenia that is associated with the pathogenesis of autoimmune diabetes. Lack of Ian4 in T cells causes mitochondrial dysfunction, increased mitochondrial levels of stress-inducible chaperonins and a leucine-rich protein, and spontaneous apoptosis of T cells. T-cell activation and caspase-8 inhibition both prevented apoptosis, whereas transfection of T cells with Ian4-specific small-interfering RNA induced apoptosis. These data suggest that Ian4-dependent proapoptotic events are active in thymocytes and may be responsible for autoimmune diabetes (Pandarpurkar et al., 2003).

In mouse thymic lymphoma 3SB cells expressing wild-type p53, ionizing radiation and UV light are potent triggers of caspase-3–dependent apoptosis. Although cytochrome c is released from mitochondria, caspase-9 activation is not observed following UV exposure. Instead UV light triggers the extrinsic apoptotic pathway and caspase-8 activation, which leads to Bid-mediated cytochrome c release from mitochondria. Thus, the postmitochondrial apoptotic (intrinsic) pathway downstream of cytochrome c release cannot mediate the apoptosome function in

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**Fig. 2.** Thymus-related medical conditions. The hypertrophic or hypotrophic thymus can be the consequence of different pathologies. Thymomas are often associated with either autoimmunity or immunodeficiency (myasthenia gravis, pure red cell aplasia [PRCA], hypogammaglobulinemia, Good’s syndrome, or autoimmune polyglandular syndrome type 1 [APS-1]). A hypotrophic thymus is the consequence of diseases, such as cancers, acute infections, and GVHD, or physiologic conditions, such as aging.

**Fig. 3.** Importance of caspase (Casp)-8 in the sensitization of cancer cells to chemotherapy. On the left side, a cancer cell resistant to a chemotherapeutic DNA damaging agent in which the caspase-8 pathway is not activated (light gray dotted arrows, left). The same cancer cell treated sequentially with a chemotherapeutic DNA damaging agent (time 1) followed by an epidermal growth factor receptor (EGFR)–inhibiting agent (time 2). This cell becomes highly sensitive to apoptosis and has low tumorigenicity (light gray dotted lines) owing to activation of the caspase-8 pathway.
UV-induced apoptosis in thymic 3SB cells (Okamoto et al., 2010).

Thymic graft-versus-host disease (tGVHD) can contribute to profound T-cell deficiency and repertoire restriction after allogeneic bone marrow transplantation (allo-BMT). However, the cellular mechanism underlying tGVHD and the interactions between donor alloreactive T cells and thymic tissues remain poorly defined. Using clinically relevant murine allogeneic BMT models, studies have shown that low numbers of donor alloreactive T cells, which caused mild nonlethal systemic GVHD, were sufficient to damage the thymus, delay T-lineage reconstitution, and compromise donor peripheral T-cell function. Radiation in BMT conditioning regimens can upregulate the expression of Fas and death receptor 5 on thymic stromal cells (especially the epithelium), and decrease expression of the antiapoptotic regulator of cellular caspase-8–like inhibitory protein. tGVHD can be mediated by interaction of donor alloreactive T cells with FasL and tumor necrosis factor (TNF)–related apoptosis–inducing ligand (TRAIL) but not by TNF or perforin, thereby disrupting thymic stromal cells, cytoarchitecture, and function (Na et al., 2010).

### Thymus Pharmacology

The thymus has been the target of numerous therapeutics designed to treat the aforementioned disease conditions. For example, a therapy that targets the thymus can be an important cause of immunosuppression. Antibodies against thymocytes [antithymocyte globulin (ATG)] are raised in rabbits (rATG) or horses. rATG is used in combination with cyclophosphamide as part of a nonmyeloablative transplant regimen (Burt et al., 2013) following autologous hematopoietic stem-cell transplantation in patients with systemic sclerosis. This antibody is also used with fludarabine for reduced-intensity conditioning in matched hematopoietic stem-cell transplantation in patients with chronic granulomatous disease (Güngör et al., 2013). Interestingly, the response elicited by horse ATG and survival of aplastic anemia patients are far superior compared with rATG treatment (European Blood and Marrow Transplant Group, 2011).

### Pharmacological and Toxicological Induction of Caspase-8–Dependent Thymic Apoptosis

Targeting the caspase-8 pathway can be an important element in treating thymomas and rendering chemotherapy-resistant thymomas more responsive to chemotherapeutic agents. Therefore, many compounds have been developed for these purposes (Table 1).

**Immunomodulators.** Glucocorticoids (GC) are well established inducers of apoptosis in the thymus. Caspase-8 has been implicated in this process (Pozzesi et al., 2014) along with Gilz, which is upregulated by GCs in thymocytes. Recently, Gilz has been demonstrated to be involved in regulating T-helper cell differentiation (Cannarile et al., 2009) and controlling malignant transformation through inhibition of Ras-driven tumorigenesis (Ayroldi and Riccardi, 2009, 2012). In the thymus, GC-induced expression of Gilz is strictly linked to caspase-8 expression and activation, suggesting a feedback loop between Gilz and caspase-8 that begins with GC-mediated Gilz transcription. Once expressed, Gilz induces caspase-8 activation, which in turn promotes Gilz maintenance through its sumoylation and subsequent inhibition of ubiquitination/proteasomal degradation (Delfino et al., 2011b). Thus, Gilz protein levels are dependent on both GC-dependent regulation of Gilz transcription and caspase-8 activation (Pozzesi et al., 2014).

Cannabinoids (CBs) are known to interact with CB1 and CB2 receptors expressed in the nervous and immune systems, respectively. These compounds mediate a wide range of effects, including anti-inflammatory ones. Studies have shown that JWH-015 [(2-methyl-1-propyl-1H-indol-3-yl)-1-naphthalenylmethanone], a synthetic CB2-selective agonist, can trigger thymocyte apoptosis in vitro. JWH-015 induced cross-talk between the extrinsic and intrinsic pathways of apoptosis by involving caspase-8, -9, and -3, thereby leading to loss of mitochondrial membrane potential. Finally, JWH-015 administration in vivo caused thymic atrophy. Taken together, data from this study suggest that CB2-selective agonists, devoid of any psychotropic effect, may serve as novel anti-inflammatory/immunosuppressive agents (Lombard et al., 2007).

The treatment of rat thymocytes with terfenadine (an antiallergy drug) resulted in a dramatic increase in DNA fragmentation.

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**TABLE 1**

Effect of different compounds on caspase-8 pathway

<table>
<thead>
<tr>
<th>Compound</th>
<th>Caspase-8 Pathway Activation</th>
<th>Caspase-8 Pathway Inhibition</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>+</td>
<td>+</td>
<td>Aryoldi et al., 2009, 2012; Cannarile et al., 2009; Delfino et al., 2011a,b; Pozzesi et al., 2014</td>
</tr>
<tr>
<td>1,4-B</td>
<td></td>
<td>+</td>
<td>Marchetti et al., 2002; Fringuelli et al., 2003</td>
</tr>
<tr>
<td>Curcumin</td>
<td>+</td>
<td></td>
<td>Bhattacharyya et al., 2007a,b</td>
</tr>
<tr>
<td>YO-2</td>
<td>+</td>
<td></td>
<td>Lee et al., 2002, 2012</td>
</tr>
<tr>
<td>EtxB</td>
<td>+</td>
<td></td>
<td>Salmond et al., 2002</td>
</tr>
<tr>
<td>Indoleamine 2,3-dioxygenase</td>
<td>+</td>
<td>+</td>
<td>Fallarino et al., 2002</td>
</tr>
<tr>
<td>E2</td>
<td>+</td>
<td></td>
<td>Do et al., 2002</td>
</tr>
<tr>
<td>Nickel(II)</td>
<td>+</td>
<td></td>
<td>Kim et al., 2002</td>
</tr>
<tr>
<td>γ-TQ</td>
<td>+</td>
<td></td>
<td>Calviello et al., 2003</td>
</tr>
<tr>
<td>Etoposide</td>
<td>+</td>
<td></td>
<td>Boesen-de Cock et al., 1998</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>+/−</td>
<td></td>
<td>Enomoto et al., 2004</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>+</td>
<td></td>
<td>Lombard et al., 2007</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>+</td>
<td></td>
<td>Fujikawa et al., 2007</td>
</tr>
<tr>
<td>Geldanamycin</td>
<td>+</td>
<td></td>
<td>Ohta et al., 2007</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>−</td>
<td></td>
<td>Strauss et al., 2008</td>
</tr>
<tr>
<td>Lipopolysaccharide</td>
<td>−</td>
<td></td>
<td>Xiang et al., 2008</td>
</tr>
<tr>
<td>Organotin compounds</td>
<td>+</td>
<td></td>
<td>Tomiyama et al., 2009</td>
</tr>
<tr>
<td>5AzC</td>
<td>+</td>
<td></td>
<td>Tochitani et al., 2011</td>
</tr>
<tr>
<td>Trp-P-1</td>
<td>+</td>
<td></td>
<td>Hashimoto et al., 2002</td>
</tr>
</tbody>
</table>
Terfenadine stimulated caspase-8, -9, and -3-like activities in a time-dependent manner in thymocytes. The active forms of caspase-3 and -9 were detected in extracts from terfenadine-treated cells by immunoblotting using antibodies specific to caspasases; however, active caspase-8 was not detected in this fraction, suggesting that terfenadine induces apoptosis in rat thymocytes via a mitochondrial pathway (Enomoto et al., 2004).

The B subunit of *Escherichia coli* heat-labile enterotoxin (EtxB) is a potent immunomodulatory molecule capable of treating and preventing autoimmune disease. The finding that CD8+ SP thymocytes from transgenic mice expressing a dominant-negative form of I kBα were markedly less susceptible to EtxB-induced apoptosis than cells from wild-type mice indicate that nuclear factor-κB (NF-κB) is important in the induction of apoptosis. Further investigation revealed that caspase-8 is active concomitant with caspase-3, consistent with death receptor-mediated signaling. However, experiments using *lpr/lpr and p55 Tnfr−/−* mice eliminate the involvement of Fas and the p55 TNF receptor, respectively, in this process (Salmond et al., 2002).

**Chemotherapeutic Agents.** γ-Tocopheryl quinone (γ-TQ), an oxidative metabolite of gamma-tocopherol, is a potentially powerful chemotherapeutic agent since this molecule exerts powerful cytotoxic effects, induces apoptosis, and escapes drug resistance in human acute lymphoblastic leukemia and promyelocytic leukemia cells. The apoptotic potential of γ-TQ was studied in vivo in murine thymoma cells grown in ascites. γ-TQ induced apoptosis in a dose- and time-dependent manner in all cell types examined. However, HL-60 and thymoma cells exhibited greater sensitivity, possibly owing to activation of caspase-8, caspase-9, Bid, and mitochondrial cytochrome c release (Calviello et al., 2003).

The anticancer drug Etoposide induces apoptosis and, surprisingly, CD95-independent processing of caspase-8 in Jurkat cells. Consistent with this, thymocytes from CD95-deficient *lpr/lpr* mice readily undergo apoptosis in response to etoposide, indicating that CD95 is not required for etoposide-mediated caspase-8 processing and apoptosis (Boesen-de Cock et al., 1998).

1,4-Benzothiazine (1,4-B) derivatives exert numerous effects in vivo and in vitro, including neurotoxicity and antimurine cytotoxicity. Results indicate that several 1,4-B analogs can induce both thymocyte apoptosis in vitro and thymus cell loss in vivo. Moreover, in vitro experiments have shown that 1,4-B-induced apoptosis is associated with different biochemical events, including phosphatidylcholine-specific phospholipase C activation, acidic sphingomyelinase activation and ceramide generation, loss of mitochondrial membrane potential and cytochrome c release, and caspase-8, -9, and -3 activation (Marchetti et al., 2002). Removal of the alcohol group by dehydration of olefin or transformation into ether increases the apoptotic activity of 1,4-B. Analogs of this compound activate caspase-8, and their structural properties correlate with those required for inducing apoptosis (Pringuelli et al., 2003).

Tumors induce thymic atrophy to evade the cellular immune response. Severe thymic hypocellularity, along with decreased thymic integrity, has been observed in tumor patients. Studies have shown that tumor-induced oxidative stress plays a critical role in thymic atrophy. This effect resulted from perturbation of NF-κB activity by increasing cytosolic IkBα retention, which inhibited NF-κB nuclear translocation in thymic T cells. These cells are vulnerable to tumor-secreted TNF-α, which mediates apoptosis by activating TNF receptor–associated protein death domain–associated, FADD, and caspase-8. Curcumin prevents tumor-induced thymic atrophy by restoring NF-κB activity. Thus, these results suggest that, unlike many other anticancer agents, curcumin is not only devoid of immunosuppressive effects but can in fact restore immunity in tumor patients (Bhattacharyya et al., 2007b).

Cyclophosphamide (CY), a DNA-damaging drug, is widely used to treat hematologic malignancies and autoimmune disorders. However, the molecular mechanism of apoptosis induction by CY remains largely unknown. Z-Val-Ala-Asp-fluoromethylketone (Z-VAL-FMK) did not inhibit thymocyte and splenocyte depletion after CY treatment in mice. Caspase-8 and receptor-induced protein were dispensable for 4-OH-CY–mediated apoptosis, whereas overexpression of Bcl-2 was partially protective. These results strongly indicate that oxidative damage–induced nuclear translocation of apoptosis-inducing factor and endonuclease G in 4-OH-CY–treated cells may represent an alternative death pathway in the absence of caspase activity (Strauss et al., 2008).

5-Azacytidine (5AzC) is a cytidine analog that causes DNA damage, which results in apoptosis, and DNA hypomethylation, which restores normal cell growth and differentiation. Treatment with 5AzC increased the frequency of terminal deoxynucleotidyl transferase–mediated digoxigenin-deoxyuridine nick-end labeling–positive thymocytes and level of cleaved caspase-3 protein, two features of apoptosis. 5AzC-induced apoptosis was even observed in the thymus of mice deficient in p53, a critical factor in the intrinsic apoptotic pathway. Moreover, mice harboring a mutation in the gene encoding Fas exhibited enhanced apoptosis. Following 5AzC treatment, the level of cleaved caspase-8 increased with cleavage of its target protein, Bid. Moreover, the level of TRAIL protein, which induces apoptosis through caspase-8 cleavage, increased dramatically in the thymus of 5AzC-treated animals. In conclusion, 5AzC-induced apoptosis of thymocytes in vivo is mediated by the extrinsic pathway and TRAIL activation (Tochitani et al., 2011).

**Enzymes and Enzyme Inhibitors.** Treatment of rat thymocytes with YO-2 [trans-aminomethylcyclohexanecarboxyl-1-O-(picolyl)tyrosine-octylamide], a novel inhibitor of plasmin, results in increased DNA fragmentation and, therefore, increased thymocyte apoptosis. Plasmin inhibitory activity may play an important role in YO-2–induced apoptosis. Furthermore, stimulation of caspase-8, -9, and -3-like activities has been observed in thymocytes treated with YO-2 (Lee et al., 2002).

Indoleamine 2,3-dioxygenase is a tryptophan-catabolizing enzyme with regulatory effects on T cells resulting from tryptophan depletion in specific tissue microenvironments. Tryptophan metabolites in the kynurenine pathway, such as 3-hydroxyanthranilic and quinolinic acids, induce selective apoptosis of murine thymocytes in vitro. Relatively low concentrations of kynurenines can induce T-cell apoptosis that does not require Fas/FasL interactions and is associated with caspase-8 activation and mitochondrial cytochrome c release. When administered in vivo, these two kynurenines can deplete specific thymocyte subsets similarly to dexamethasone (Fallarino et al., 2002).

β-Estradiol-17-valerate (E2) induces thymic apoptosis and decreases thymic cellularity. Interestingly, however, the extent of thymic atrophy in *lpr/lpr* (Fas-negative) and *gld/gld* (FasL-negative) mice was significantly less than that seen in wild-type mice. A caspase-8 inhibitor blocked E2-induced apoptosis...
administration of DBTC or TBTC; the magnitude of this effect over a 4-day treatment period differed between the two agents. TBTC exposure induced apoptosis and caused a marked increase in caspase-8, -9, and -3 activity, whereas DBTC exposure induced necrosis without any significant change in caspase activity. Therefore, these results indicate that increased cell death induced by organotin compounds probably contributed to the thymic atrophy observed in the rats (Tomiyama et al., 2009).

**Discussion**

In this review, we dissected the pharmacological modulation of caspase-8 in the thymus from the perspective of treating diseases by inducing caspase-8-dependent apoptosis. Despite ubiquitous expression of caspase-8 throughout the body, which raises the possibility of widespread side effects, modulation of its activation may be selectively important for immunity because its genetic absence results in immunodeficiency disease (Pozzesi et al., 2014). Furthermore, targeting caspase-8 activation could be effective in treating and preventing thymic atrophy, which is the hallmark of extrathymic medical conditions, such as acute infections (Farias-de-Oliveira et al., 2013), cancer (Bhattacharyya et al., 2007a, b), and tGvHD (Na et al., 2010), or aging (Aspinall et al., 2010). The current trend in research focuses on discovering regenerative therapies (Boehm and Swann, 2013); however, preventing thymic atrophy by inhibiting caspase-8-dependent apoptosis could be an effective strategy for improving and prolonging thymus function.

**Authorship Contributions**

Wrote or contributed to the writing of the manuscript: Pozzesi, Fierabracci, Thuy, Martelli, Liberati, Ayrolld, Riccardi, Delfino.

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