Autoimmunity Reviews 13 (2014) 231–241

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

# Recent insights on the putative role of autophagy in autoimmune diseases

Elena Gianchecchi [a], Domenico Vittorio Delfino [b], Alessandra Fierabracci [a,*]

[a] Autoimmunity Laboratory, Immunology Area, Bambino Gesù Children's Hospital IRCCS, Rome, Italy
[b] Section of Pharmacology, Toxicology and Chemotherapy, Department of Clinical and Experimental Medicine, Perugia University, Perugia, Italy

ARTICLE INFO

*Article history:*
Received 1 October 2013
Accepted 15 October 2013
Available online 1 November 2013

*Keywords:*
Autoimmunity
Etiopathogenesis
Autophagy
Candidate autoimmune genes
Innate/adaptive immune system

ABSTRACT

The incidence of autoimmune pathologies is increasing worldwide. This has stimulated interest on their etiopathogenesis, caused by a complex interaction of genetic and environmental factors. With the advent of genome-wide linkage, candidate gene and genome wide association studies, risk polymorphisms in autophagy-related genes were discovered in several autoimmune conditions suggesting the possible contribution of autophagy to their etiopathogenesis. Autophagy represents the principal catabolic process mediated by lysosomes used by eukaryotic cells and is strictly regulated by proteins belonging to the *Atg* family. The function of autophagy has been well characterized in various tissues and systems, but its role in the regulation of innate and adaptive immune systems has been only recently discovered. It plays a fundamental role in the modulation of thymocyte selection and in the generation of T lymphocyte repertoire by participating in the intracellular antigen presentation on MHC class-II molecules by thymic epithelial cells. Furthermore, the generation of mice with knockout for specific autophagy-related genes induced several immunological alterations, including defects in B and T cell compartments and in T cell activation. In this review we report recent evidence on the role of autophagy in autoimmunity and discuss its relevance to the pathogenesis of these diseases. We finally highlight that future research may disclose potential new therapeutic targets for the treatment of this category of disorders by modulating the autophagic pathway.


**Contents**



* Corresponding author at: Bambino Gesù Children's Hospital IRCCS, Piazza S. Onofrio 4, 00165 Rome, Italy. Tel.: +39 06 6859 2656; fax: +39 06 6859 2904.
*E-mail address:* alessandra.fierabracci@opbg.net (A. Fierabracci).

1568-9972/$ – see front matter 
http://dx.doi.org/10.1016/j.autrev.2013.10.007

## 1. Introduction

Autoimmune diseases are a heterogeneous group of 'common complex disorders' [1] affecting various organs or systems. An interaction of genetic and environmental factors underlies their etiopathogenesis [2]. Over the past 30 years an increased incidence of autoimmune disorders has been reported worldwide [2]; overall they affect approximately 5% of the population (reviewed (rev.) [3]) and frequently patients affected by one autoimmune disease have an increased susceptibility to develop other autoimmune manifestations (rev. in [4]).

The clinical onset of disease is often preceded by a long preclinical period as best exemplified by the natural history of insulin-dependent diabetes mellitus [Type 1 diabetes (T1D)] [5]. Predictive strategies of disease onset are therefore aimed at detecting immunological abnormalities in the peripheral blood such as detection of circulating autoantibodies together with assessing genetic risk factors in family and population screenings.

It is generally recognized that autoimmunity derives from the escape of antigen-specific autoreactive T cells in the periphery from the thymus in the perinatal age [4] due to a failure to promiscuous thymic expression of peripheral organ-specific antigens in the same organ (rev. in [4]). In the autoimmune process T helper (Th) cells [6], that escaped mechanisms of self-tolerance, initiate inflammation and provide help to autoreactive B cells [7] mediated by pro-inflammatory cytokines. The activation, expansion and subsequent differentiation of mature B cells in plasma cells producing autoantibodies further contribute to tissue damage.

Information regarding the etiopathogenesis of autoimmunity has rapidly increased with the advances in immunogenetics over the past years [4]. As recently shown by genetic mapping studies, multiple genetic loci are responsible for T1D, systemic lupus erythematosus (SLE), multiple sclerosis (MS), inflammatory bowel disease (IBD), rheumatoid arthritis (RA) and psoriasis.

A common genetic allele association was first reported in the 1970s with the major histocompatibility complex (MHC) region encoding for human leukocyte antigens (HLAs) [8] in autoimmune conditions where multiple subtypes are involved [9]. In addition to HLA, several single nucleotide polymorphisms (SNPs) possibly underlie the pathogenesis of autoimmunity [3] as shown in subsequent genome wide linkage, candidate gene and genome wide association (GWA) studies. Candidate common susceptibility genes involved in immune regulation include cytotoxic T lymphocyte-associated antigen 4 (*CTLA-4*) that suppresses T cell activation, forkhead box protein 3 (*FoxP3*) playing a role in T regulatory cell (Treg) differentiation, the *IL-2Rα*/*CD25* gene affecting the development and function of Tregs, and the tumor necrosis factor alpha (*TNF-α*) gene. Among the others, protein tyrosine phosphatase non-receptor type 22 (*PTPN22*), encoding for the lymphoid tyrosine phosphatase (Lyp) protein, affects the T cell receptor (TCR) signaling pathway (rev. in [9]).

In recent years new mechanisms regulating immunological tolerance and autoimmunity were discovered with a special focus on genes controlling the proteolytic pathways involved in antigen presentation [10]. In the autoimmune process, immune responses are generated against peptides which are presented in the context of MHC class I molecules. MHC antigen processing and presentation lead to the formation of these complexes in the endoplasmic reticulum (ER). MHC class I binding peptides are produced in the cytoplasm by degradation of endogenous proteins; this occurs through proteases including the multicatalytic proteasome [11]. The transporters associated with antigen processing (TAP1 and TAP2) transport some proteolytic intermediates into the ER for further processing by ER aminopeptidases, ERAP1 and ERAP2, before being loaded onto MHC class I molecules [4]. GWA and follow-up-case control studies leading to ERAP SNP identification in several autoimmune conditions were conducted. Close linkages have been found in a number of diseases, including ankylosing spondylitis (AS), MS, Crohn's disease (CD) and T1D. Furthermore cross-talk among different proteolytic pathways was highlighted *i.e.* components processed in the ubiquitin/proteasome system possibly engaged in autophagic pathways [12]. Several genetic studies have already displayed the involvement of various risk polymorphisms in autophagy-related genes in the autoimmune process. This basic knowledge underlies the relevance of clarifying the putative pathogenetic role of proteolytic pathways such as the autophagic pathway in autoimmunity. In this review we report recent evidence on the role of autophagy in autoimmunity and discuss its relevance to the pathogenesis of these diseases. We finally highlight that research on autophagy may disclose potential new therapeutic targets in this category of disorders.

## 2. What is autophagy?

In eukaryotic cells two mechanisms are available for breaking down intracellular components: proteasomes and autophagy [13]. Autophagy constitutes the principal regulated catabolic process mediated by lysosomes used by eukaryotic cells. Three forms of autophagy can be distinguished on the basis of their cell functions and modality of cytoplasmic cargo transport to lysosomes: chaperone-mediated autophagy, microautophagy, and macroautophagy (which is discussed in this review and herein referred as autophagy) [14,15]. Such mechanism is present at low basal level in all cell types [14].

Autophagy consists in the entrapment of intra-cytoplasmic material by double-membrane vesicles defined as autophagosomes [16,17]. The fusion of autophagosome with lysosomes causes the generation of autolysosomes in which the sequestered materials and the inner membrane are degraded [14] by lysosomal hydrolases [18].

The origin of the autophagosomal membrane (isolation membrane) is not fully elucidated [18]. Membranes of several structures and organelles, such as ER, mitochondria (19 rev. in [20]), the Golgi apparatus, post-Golgi compartments [20], nucleus and plasma membranes [19] (rev. in [20]) contribute to autophagosome formation. However the question is at the moment not completely elucidated since protein markers selective for the previous cited organelles [20] are lost during autophagosomal formation.

Autophagy is genetically regulated and its morphology has been well characterized both in yeasts and mammalians [16]. The autophagic process is regulated by proteins belonging to the autophagy-related gene (*Atg*) family [16,18,21,22]. Atg proteins are evolutionary conserved from yeasts to mammals [18]. Each of them exerts a specific function during the autophagy process [21] which consists of four phases, from the formation of the autophagosome, its subsequent elongation, the targeting to lysosomes and finally their fusion (*vide supra*) [23,24].

The process of autophagy occurs through the inactivation of the mammalian target of rapamycin complex 1 (mTORC1), also defined as "mechanistic target of rapamycin" [18], which is a nutrient sensing conserved serine/threonine kinase [18,21]. This inactivation occurs by hypoxia, starvation [18,21] and rapamycin pharmacological treatment [18]. Nevertheless independent mechanisms other than mTORC1 were also reported [18,24–27].

## 3. The autophagic pathway

In mammalian cells the autophagosome formation is strictly regulated by the Unc51-like kinase 1 (ULK1) complex activated by the dissociation of mTORC1 which is constituted by mTOR, regulatory associated protein of mTOR (raptor), proline-rich AKT substrate 40 kDa (PRAS40), G protein β subunit-like protein (GβL/mLST8) and DEP domain containing mTOR-interacting protein (DEPTOR) (*vide supra*) [18] (Fig. 1). ULK1 complex is formed by ULK1/2, Atg13, Atg101 and the focal adhesion kinase family interacting protein of 200 kDa (FIP200). ULK1 complex moves into the autophagosomal formation site. Subsequently this event leads to the dephosphorylation of Atg13, ULK1 and ULK2 inducing the activation of these two last kinases. Subsequently ULK1 and ULK2 activation causes the phosphorylation of FIP200 and Atg13.