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REVIEW

Autophagopathies: from autophagy gene polymorphisms to precision medicine for human diseases

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ABSTRACT

At a time when complex diseases affect globally 280 million people and claim 14 million lives every year, there is an urgent need to rapidly increase our knowledge into their underlying etiologies. Though critical in identifying the people at risk, the causal environmental factors (microbiome and/or pollutants) and the affected pathophysiological mechanisms are not well understood. Herein, we consider the variations of autophagy-related (*ATG*) genes at the heart of mechanisms of increased susceptibility to environmental stress. A comprehensive autophagy genomic resource is presented with 263 single nucleotide polymorphisms (SNPs) for 69 autophagy-related genes associated with 117 autoimmune, inflammatory, infectious, cardiovascular, neurological, respiratory, and endocrine diseases. We thus propose the term 'autophagopathies' to group together a class of complex human diseases the etiology of which lies in a genetic defect of the autophagy machinery, whether directly related or not to an abnormal flux in autophagy, LC3-associated phagocytosis, or any associated trafficking. The future of precision medicine for common diseases will lie in our ability to exploit these *ATG* SNP x environment relationships to develop new polygenetic risk scores, new management guidelines, and optimal therapies for afflicted patients.

Abbreviations: ATG, autophagy-related; ALS-FTD, amyotrophic lateral sclerosis-frontotemporal dementia; ccRCC, clear cell renal cell carcinoma; CD, Crohn disease; COPD, chronic obstructive pulmonary disease; eQTL, expression quantitative trait loci; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; GTEx, genotype-tissue expression; GWAS, genome-wide association studies; LAP, LC3-associated phagocytosis; LC3-II, phosphatidylethanolamine conjugated form of LC3; LD, linkage disequilibrium; LUAD, lung adenocarcinoma; MAF, minor allele frequency; MAP1LC3/LC3: microtubule associated protein 1 light chain 3; NSCLC, non-small cell lung cancer; OS, overall survival; PtdIns3K CIII, class III phosphatidylinositol 3 kinase; PtdIns3P, phosphatidylinositol-3-phosphate; SLE, systemic lupus erythematosus; SNPs, single-nucleotide polymorphisms; mQTL, methylation quantitative trait loci; ULK, unc-51 like autophagy activating kinase; UTRs, untranslated regions; WHO, World Health Organization.

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The rising incidence of complex illnesses and their costs have revolutionized basic research needs and approaches, but also patient management, and societal needs. Between 70 to 90% of the risk of developing a disease is due to the air we breathe, the water we drink, the diet we eat, and the surroundings in which we work and live [1]. Visibly polluted, infected, or not, the fact remains that we are now more than ever exposed to environmental risks. Thus, an unhealthy environment can be considered as a pandemic, affecting 280 million people worldwide and claiming 14 million deaths every year from hundreds of diseases, including neurodegenerative, autoimmune, inflammatory illnesses, and cancer [2]. Though critical in identifying the people at risk, the causal environment components (pathogens and/or pollutants) and the compromised

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Supplemental data for this article can be accessed here.

physiological mechanisms are not yet well understood. When it comes to environmental stress, we are not equal. However, presented with the same environment, regardless of the pathogens and pollutants we are challenged with, only a small fraction of individuals will develop pathologies. We thus reasoned that the efficiency of our inherited "environmental response machinery" may determine our susceptibility to illness.

Introduction

A. Overview of the autophagy pathway: an immediate cellular response to environmental challenges

Among the many mechanistic pathways, we focus on macroautophagy (hereafter referred to as autophagy), a homeostatic pathway that also provides an immediate adaptive cellular response to environmental injury that ensures cell repair [3]. As suggested by its name (auto = self; phagy = eating), autophagy enables, in all eukaryotic cell types, the turnover of all organelles and most long-lived proteins by a pathway that begins with the formation of a double-membrane compartment, termed a "phagophore," which captures these components from the cytosol. The phagophore expands into a completed vesicle, an "autophagosome." Subsequently, the autophagosome rapidly fuses with a lysosome to become an "autolysosome," in which the content is finally degraded. Successful completion of autophagy requires the coordinated orchestration of more than 69 different autophagy-related (ATG) and other proteins as well as regulators acting at different steps of the process, namely:

(1) ULK (unc-51 like autophagy activating kinase) complex (ULK1, ULK2, ATG13, RB1CC1/FIP200, and ATG101) initiates the induction step.
(2) Once activated, ULK1 phosphorylates BECN1 and ATG14, two components of the class III phosphatidylinositol 3-kinase (PtdIns3K CIII) complex (PIK3C3/VPS34, PIK3R4/VPS15, ATG14, BECN1, and NRBF2), thereby enhancing PIK3C3 activity and phagophore membrane formation.
(3) WIPI1 (WD repeat domain, phosphoinositide interacting 1) and WIPI2 bind phosphatidylinositol-3-phosphate (PtdIns3P), generated by the PtdIns3K CIII; these effectors then recruit ATG16L1 that mediates phagophore expansion through ubiquitination-like reactions.
(4) In the first ubiquitination-like reaction, ATG5 and ATG12 are conjugated to each other in the presence of ATG7 and ATG10. The attachment of the complex containing ATG5, ATG12, and ATG16L1 on the phagophore membrane induces the second complex to covalently conjugate phosphatidylethanolamine to LC3 (LC3-II), which facilitates closure of the phagophore into the autophagosome.
(5) ATG9 (the ATG9-ATG2-WIPI1/Atg18 complex) is another factor essential for expanding the phagophore, which cycles between endosomes, the Golgi, and the phagophore; ATG9 is a lipid scramblase that functions along with ATG2 to transfer lipid components for membrane expansion.
(6) ATG4 first primes LC3 for conjugation, and later removes LC3-II from the outer surface of newly formed autophagosomes; LC3 on the inner surface is eventually degraded when the autophagosome fuses with a lysosome.
(7) The fusion between an autophagosome and a lysosome involves several proteins, including LAMP, RAB7, and the second complex of PtdIns3K CIII (PIK3R4, PIK3C3, UVRAG, and BECN1), resulting in vesicle breakdown and cargo degradation into autolysosomes by lysosomal hydrolases.
(8) Under both baseline conditions and times of stress, several autophagic receptors (including SQSTM1/p62, NBR1, CALCOCO2/NDP52, OPTN, DRAM1, WDFY3/ALFY, and TOLLIP) are recruited to recognize and facilitate the selective elimination of ubiquitinated protein aggregates and damaged/dysfunctional organelles by sequestration within autophagosomes; these aggregates and organelles would otherwise accumulate during the life of the cell (Figure 1).

Throughout development and life, autophagy is required for the maintenance, self-renewal, and differentiation of stem-like cells, such as in the hematopoietic system. Likewise, such an intracellular 'renewal' (i.e., recycling) process also plays an essential role in determining the homeostasis, functionality, and longevity of post-mitotic cells such as cardiomyocytes and neurons. In a state of emergency, exposure of all cell types to environmental challenges as varied as nutrient starvation, pathogens, and chemical pollutants massively and transiently upregulates the entire autophagy machinery to repair cells and meet their energy needs. Such an intricate interplay between autophagy and the environment is essential for cell/individuals' adaptation to changing conditions and, when impaired, predisposes to disease.

B. The long and winding road from ATG variations to disease susceptibility

Over the last twenty years, the completion of the human genome project and the remarkable progress of the genome-wide association study (GWAS) have accelerated the identification of hundreds of susceptibility loci for diseases, some of which concern autophagy-related genes. In December 2021, a PubMed search for "autophagy AND (susceptibility OR polymorphism OR SNP OR variant OR variation OR mutation)" yielded 9,076 entries. 243 relevant studies totaling 3,504,075 participants (2 million patients and 1.5 million controls) – 77 are GWAS – have identified 263 common SNPs for 69 *ATG* genes associated with 185 autoimmune, inflammatory, cardiovascular, neurological, and lung diseases and traits; all are common complex diseases.

We conducted a comprehensive survey of this *ATG* SNP list using the dbSNP (https://www.ncbi.nlm.nih.gov/snp/) [4], LitVar (https://www.ncbi.nlm.nih.gov/CBBresearch/Lu/Demo/LitVar/) [5], HaploReg (https://pubs.Broad-institute.org/mammals/haploreg/haploreg.php, v4.1) [6], and GTEx

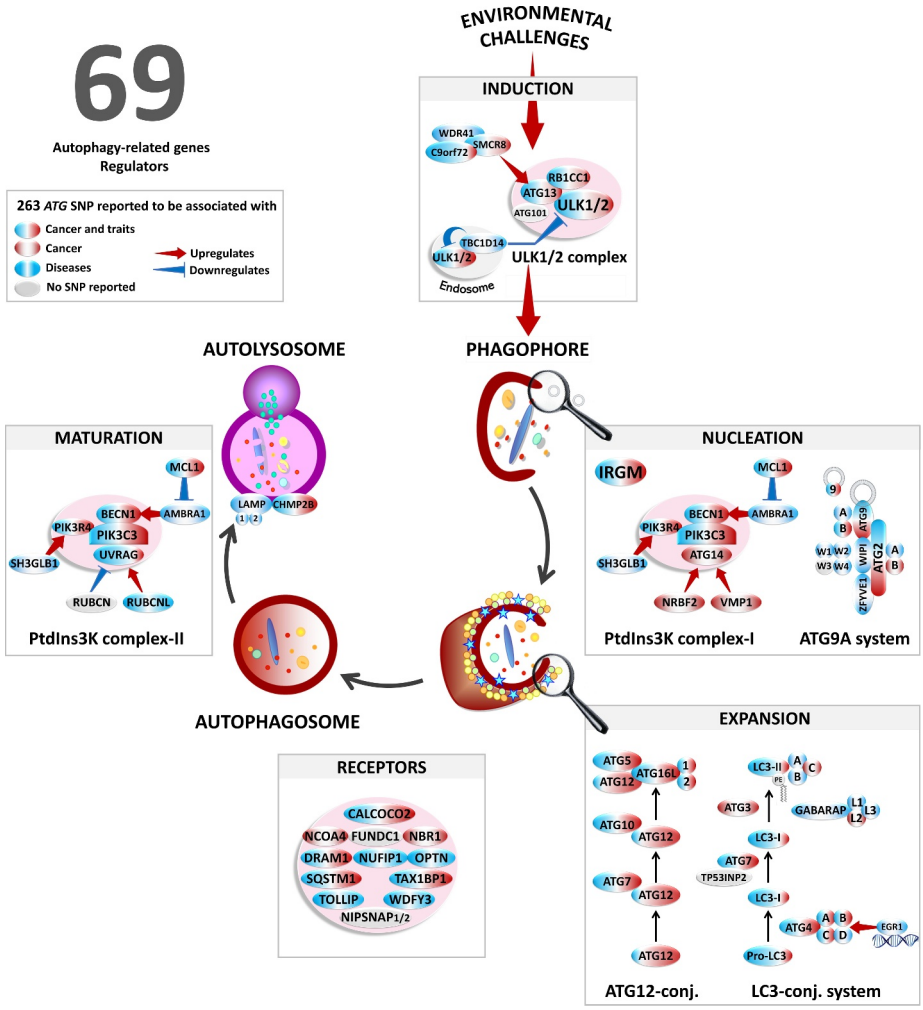

Figure 1. Overview of the autophagy pathway in response to environmental challenges. Schematic illustrating the molecular machinery of autophagy including the major autophagy-related proteins and complexes. Associations of *ATG* polymorphisms with cancers (red) and non-cancer diseases (blue).

(Genotype-Tissue Expression; https://www.gtexportal.org/home/v8-release) [7] public databases:

i) The variety of defects in autophagy that are involved in human pathogenesis resulting in disease initiation, progression, and treatment efficacy is considerable. Strikingly, most diseases are highly *polygenic*, influenced by many *ATG* variants, each giving a small effect.

ii) Rather than being a mere inventory of correlations, several *ATG* variations have pleiotropic effects affecting multiple 'apparently' unrelated diseases. Likewise, many of these SNPs have protective effects, allowing them to be maintained in the population. This *antagonistic pleiotropy* is undoubtedly related to the essential, ubiquitous, and double-edged roles of autophagy in pathologies [8]. These two features, *polygenic* and *pleiotropic* inheritances, make it challenging to identify causal SNPs [9] (see **Tables S1-S7**).

iii) The SNP-disease correlations are even more confusing as 90% of the diseases associated with *ATG* alleles localize to non-coding genomic regions (intron, intergenic, 5' and 3' untranslated regions [UTRs]). Nearly one-third are regulatory SNPs, also called expression quantitative trait loci (eQTL), associated with a difference in transcript abundance. As such, these non-coding regulatory variations can dramatically affect the rate of autophagy flux and how individuals respond to environmental stimuli. However, very few functional genomic studies have so far investigated this *ATG* SNP x environmental interaction, which represents another critical bottleneck for SNP-disease correlations.

With this in mind, the present review aims to provide the scientific and clinical community with a comprehensive autophagy genomic resource to embrace health risk assessment, precision medicine, and new potential therapeutic opportunities.

Pleiotropy: opening pandora's box

As autophagy is ubiquitous and essential for the survival of all cell types, its dysfunction can manifest like a 'constellation' of symptoms that affect any organ. Within each organ, we will briefly outline here the range of diseases associated with autophagy SNPs (Figures 2–5, **Figures S1-S3, and Tables S2-S7**). In these figures, panel A will emphasize that diseases can be inflammatory, autoimmune, degenerative (right panel), or associated with cancer (left), and influenced by environmental cues, regardless of their nature. Panel B will help to visualize the autophagic genes, the variation in which may give rise to similar clinical manifestations, i.e., the *disease module*. In keeping with this,

panel C, when included, will present some preclinical mouse models linking a dysfunction in autophagy to the pathogenesis of major complex diseases (see a review [8] for more details on C).

A. Autophagy and neurodegenerative diseases

Roughly 40 million individuals suffer worldwide from Alzheimer disease and related conditions, a burden that is expected to explode as the population ages. To tackle this public health emergency, a treatment that prevents or delays the development of these devastating diseases is a critical unmet need. Critical for therapeutic intervention, the current consensus is that autophagy is essential to prevent the aging of long-lived post-mitotic neurons. A genetic defect in autophagy may initiate these diseases, alone or with concurrent aggregate-prone mutations [8]. Over the past five decades, we have learned how autophagy degrades selectively damaged organelles and protein aggregates that would otherwise accumulate during life. Beyond these cargos, autophagy is a quality-control system that degrades the aggregate-prone mutated proteins associated with several neurodegenerative diseases (such as Huntington disease, spinocerebellar ataxia, Parkinson disease, amyotrophic lateral sclerosis [ALS], and frontotemporal dementia [FTD]).

Variant discovery. To date, 30 common risk variants have been associated with various neurological disorders, from developmental to neurodegenerative diseases (Figure 2A).

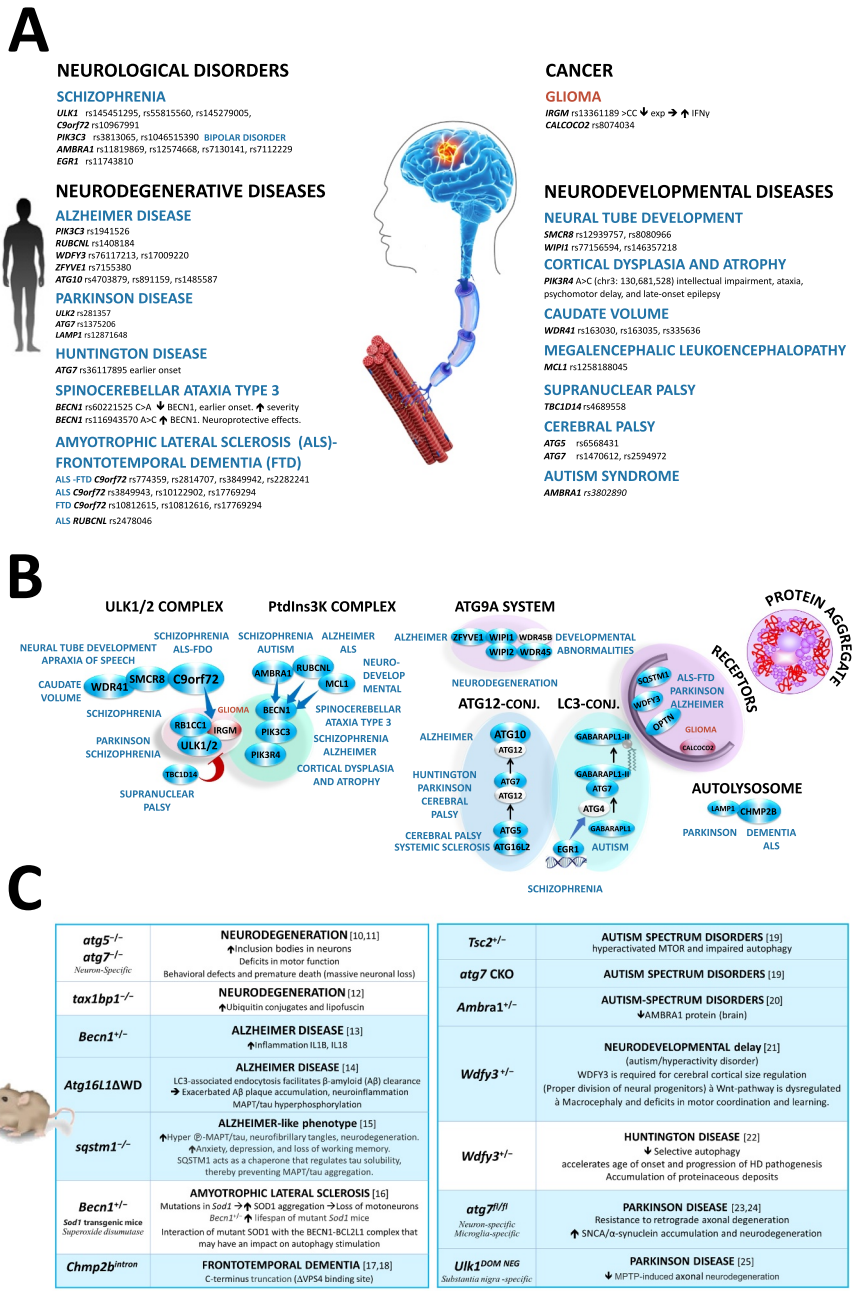

Figure 2. Deficiency in autophagy in human central nervous system diseases. (**A**) Summary of autophagy-related gene variations. (**B**) Steps of the autophagy pathway affected by SNPs. (**C**) Phenotype of autophagy-deficient mousemodels [10–25] Ⓟ-MAPT: phosphorylated-MAPT/tau.

The most striking findings include: *i*) the high *polygenic nature* of these diseases linked with five to seven *ATG* variants: For example, Alzheimer disease (*PIK3C3* [26], *RUBCNL* [27], *ZFYVE1/DFCP1* [28], *WDFY3* [29], and *ATG10* [30]), schizophrenia (*ULK1* [31], *RB1CC1* [32,33], *C9orf72* [34], *PIK3C3* [35], *AMBRA1* [36,37], and *EGR1* [38]) and Parkinson disease (*ULK2* [39], *ATG7* [40], and *LAMP1* [41]) among others. *ii*) Likewise, there is also substantial genetic *pleiotropy* across various neurological traits: *AMBRA1* with schizophrenia [36,37], and autism [42], *PIK3C3* with schizophrenia [35] and bipolar disorder [35], *ATG7* with cerebral palsy [43], Huntington disease [44], and Parkinson disease [40] (for more details see the **Tables S2-S7**).

From genetics to biology. Heritability may result from both common and rare genetic variants that affect all steps of the autophagy pathway, from autophagosome formation and substrate sequestration to lysosomal degradation (Figure 2B). For instance, ALS-FTD-linked variations are rare missense, nonsense, and truncating mutations that target the ubiquitin-binding domains of the autophagy receptors *SQSTM1* [45], *OPTN* [46], and *UBQLN2* [47], thus compromising the binding and the clearance of ubiquitinated aggregates. Similarly, other mutations are missense or whole-gene deletions of *ULK1* [31], *WIPI1* [48], *WIPI2* [49], *WDR45* [50], and *GABARAPL1* [51] that impair the formation of autophagosomes. Along these lines, several autophagy-deficient mouse models recapitulate features of neurodegenerative diseases 10-25– (Figure 2C). From a clinical perspective, these loss-of-function mutations are associated with severe neurodegenerative defects that warrant a genetic diagnosis. For the more common, late-onset forms of diseases, 36 *ATG* variations are frequent SNPs in the promoters, introns, and 3' UTR that alone confer a small risk. In the absence of a cure, we think identifying the causal *ATG* variants will be very informative for the early diagnosis and prognosis of these diseases.

B. Autophagy in infectious, autoimmune, and inflammatory diseases

More than ever, we appreciate how autophagy ensures our defense against infection with any pathogen, whether due to bacteria, viruses, parasites, or fungi. In this struggle, the autophagy pathway is essential for our survival as it immediately recognizes, captures, and kills invading pathogens through a selective process called xenophagy or virophagy when referring specifically to viruses. Beyond this innate clearance, autophagy promotes the second wave of adaptive immunity by ensuring antigen presentation to the T cells. All the survival, maturation, and effector properties of recruited troops of immune cells are controlled by autophagy 52. Upon resolution of an infection, autophagy limits the inflammatory response by the degradation of components of inflammasomes (signalphagy [53]). Thus, by orchestrating overall defense, autophagy safeguards the host against infectious, autoimmune, and chronic inflammatory diseases.

Variant Discovery. Several *ATG* variations confer enhanced susceptibility to bacteria (peritonitis: *CALCOCO2* [54]; Buruli ulcer: *ATG16L1* [55,56], leprosy: *IRGM* [57], *TOLLIP* [58,59]; *C. burnetii: ATG5* [60], *MAP1LC3A* [60]; sepsis: *ATG5* [61], *IRGM* [62], *TOLLIP* [63]; uropathogenic *E. coli: ATG16L1* [64]; and tuberculosis: *ULK1* [65,66], *ATG10* [67], *IRGM* [68–73], *TOLLIP* [74–76]), viral (human papillomavirus: *MCL1* [77]; hepatitis B virus: *ATG5* [78], *ATG16L1* [79], HIV: *TOLLIP* [80], and rhinovirus: *TOLLIP* [81,82]), and parasitic pathogens (leishmaniasis: *TOLLIP* [83]; and malaria: *TOLLIP* [84]) (Figure 3A). Regarding inflammatory bowel diseases, much has been written about Crohn disease (CD), which provides an excellent paradigm of a complex disease involving an autophagy defect. The first GWAS in 2007 highlighted *ATG16L1*, and *IRGM*, as the most robust genetic loci so far described for CD [85,86]. Since then, 8 other genes (including *ULK1, ATG2A, ATG4A, ATG4B, ATG4D, ATG5, ATG16L2*, and *CALCOCO2*) with a total of 32 SNPs have been identified. All variations influencing CD are frequent (from 4% to 53% in the general population), and most CD/variant associations are replicated across multiple ethnic groups (Figure 3B).

From genetics to biology. We focus on ATG16L1, which alone recapitulates all features of risk loci of complex diseases. ATG16L1 is part of the ATG12–ATG5-ATG16L1 trimeric complex, which defines the site where LC3 is lipidated on the nascent double-membrane autophagosomes [100]. *ATG16L1* is the target of fifteen CD-associated SNPs; all except one are eQTLs located in introns. The most extensively studied SNP is rs2241880, which leads to T300A conversion [85,86]. Despite a massive body of work, how the T300A mutation alters the function of ATG16L1 remains unclear. The existing evidence argues that it has little or no effect on constitutive or starvation-induced autophagy [101–103]. Instead, it impairs a myriad of alternative intracellular trafficking pathways involved in innate immunity, such as the trafficking of secretory vesicles in intestinal Paneth cells [88,104], and the clearance of invading bacteria by xenophagy [101,102,104,105] (Figure 3C). Faced with an emergency, ATG16L1 also mobilizes LC3 and part of the autophagy machinery to pathogen-containing phagosomes to limit infection [106]. Regardless of the pathway involved, i.e., either LC3-associated phagocytosis (LAP), xenophagy or both, the *ATG16L1* T300A mutation renders CD patients very vulnerable to bacterial infections.

From one puzzling insight to another, at the molecular level, the function of ATG16L1 in LAP relies on a C-terminal tryptophan-aspartic acid (WD)-repeat domain that is interestingly targeted by a CD-associated mutation (T300A) [107]. Of note, T300A prevents the binding of the WD domain to a transmembrane protein, TMEM59, present on the phagosome, slowing down LC3 lipidation and the LAP route [106–108]. Of interest, upon bacterial challenge, CASP3 (caspase 3) is also found to preferentially cleave the risk allele, decreasing the expression of the full-length protein, leading to impaired xenophagy [104,105]. Even more disturbing, *Atg16l1* loss in intestinal epithelial cells exacerbates chronic colitis by increasing apoptosis and/or necroptosis [109–111]. To guide new treatment options, the challenge will be to identify which of these canonical and non-canonical functions of ATG16L1 is turned off in CD.

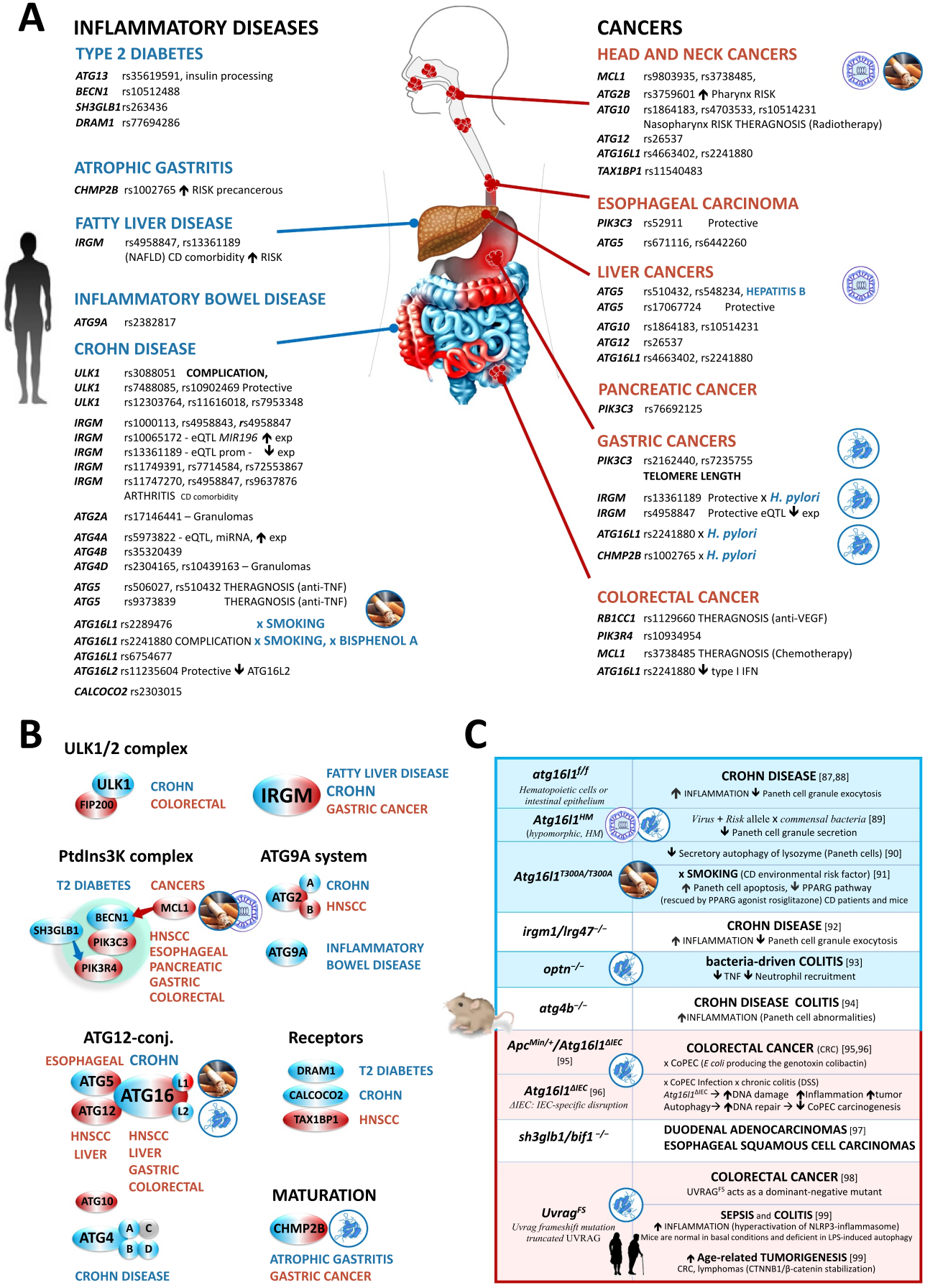

Figure 3. Deficiency in autophagy in human gastrointestinal disorders. (**A**) Summary of autophagy-related gene variations. (**B**) Steps of the autophagy pathway affected by SNPs. (**C**) Phenotypes of autophagy-deficient mouse models [87–93,93–99].

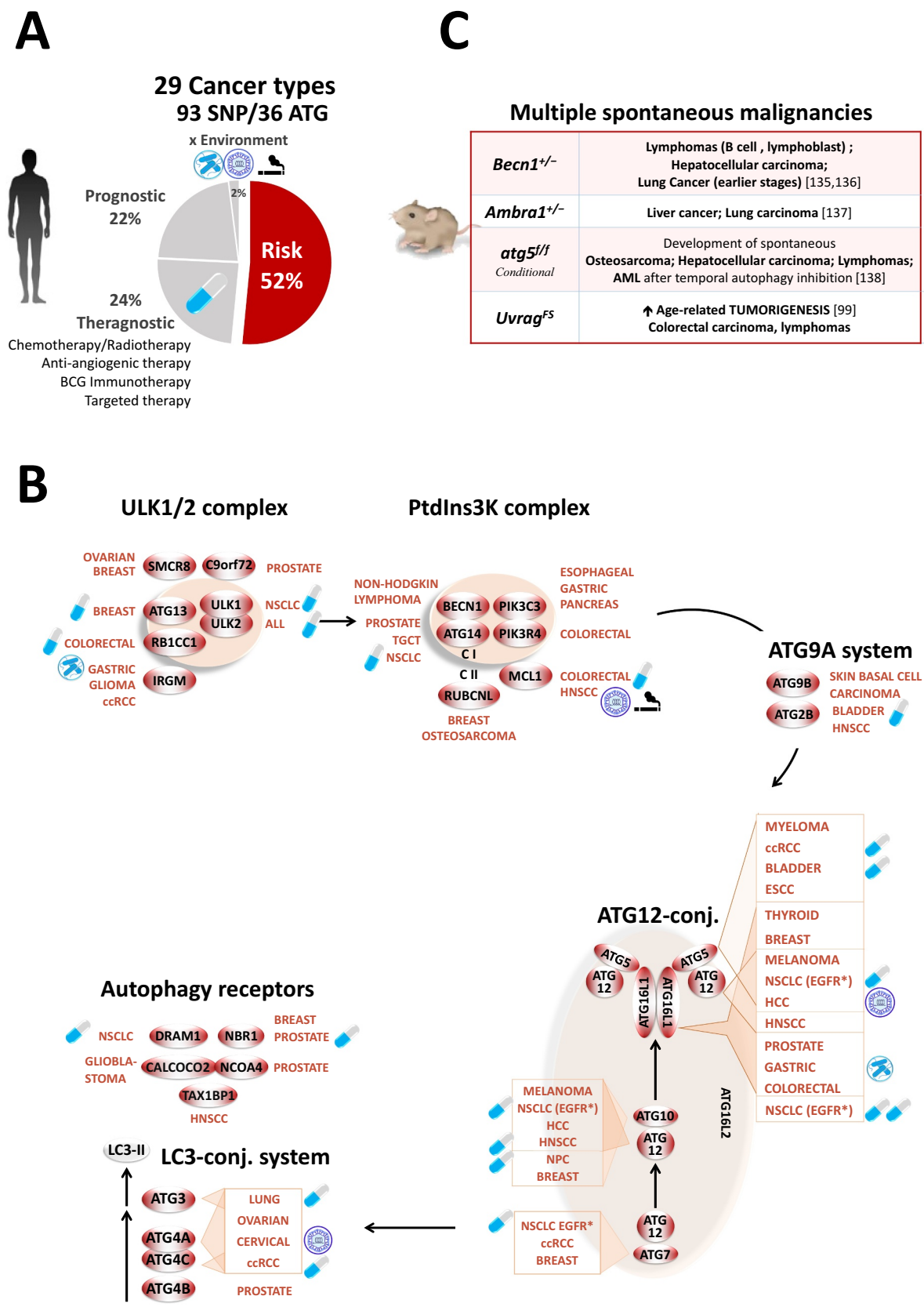

Figure 4. Landscape of *ATG* polymorphisms in human cancers. (**A**) Percentage of *ATG* polymorphisms for 29 cancer types in terms of theragnosis, prognosis, and risk, and relation with environmental factors. (**B**) Steps of the autophagy pathway affected by SNPs. ESCC, esophageal squamous cell carcinoma. (**C**) Phenotypes of autophagy-deficient mouse models [99,135–138].

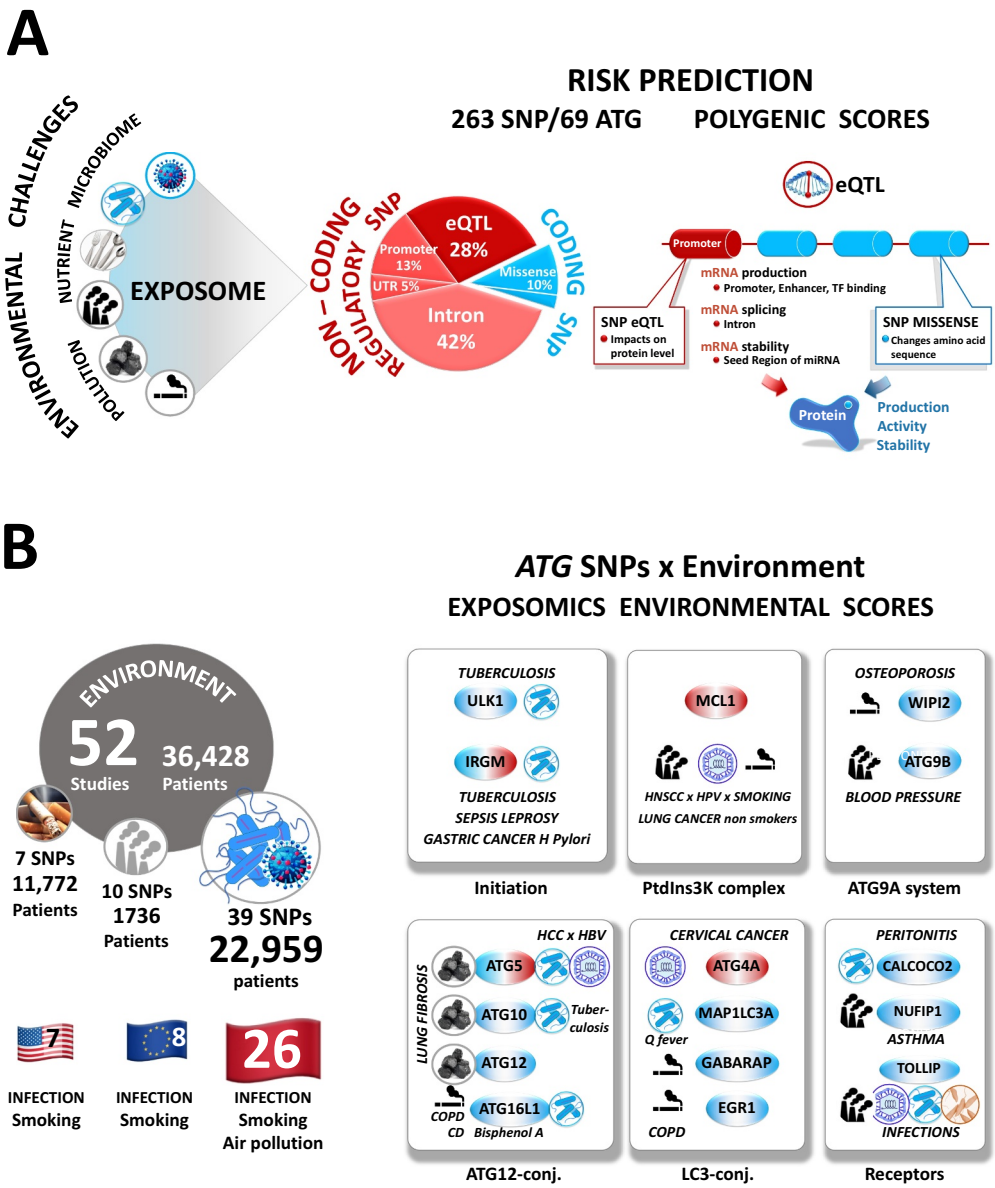

Figure 5. Biomarkers of exposure and, ultimately, of risk assessment and clinical outcome. (**A**) Right. Distribution (in percentage, *left*) and predicted functional consequences (*right*) of 219 coding and non-coding regulatory *ATG* SNPs. *Left*, Number of studies, totaling the number of patients, *ATG* genes, and SNP per Europe, United States, and Asia. Note that whereas 70 to 90% of the risk of developing a disease is due to the environment, only 13% of studies on autophagy gene SNPs have included the environment as a trigger or exacerbating factor. Likewise, air pollution is the fourth most prevalent deadly risk factor worldwide and, so far, most of the studies focused on infection. TF, transcription factor. Related to: (**B**) The concept of the exposome and atlas of the 'autophagy gene × environmental' interactions in the susceptibility of complex human diseases. Because of the long latency period, exposure to a causal agent/mixture typically occurs years to decades before disease diagnosis. The exposome is a unique marker that characterizes the totality of trace chemicals resulting from different routes (internal and external) and times of exposure over the lifetime of an individual.

C. Autophagy and cancer

More than 20,000 articles in PubMed NCBI have addressed the impact of autophagy on tumor development. However, no consensus has yet been reached, as two opposing hypotheses of pro- and anti-tumor autophagy still provoke strong controversy [112]. Indeed, some advocate that this process is harnessed by cancer cells to fuel their metabolism, prevent oxidative stress, and thus promote tumor growth and resistance to anti-tumor therapies. Others propose that autophagy can counteract malignant transformation by degrading signaling proteins, and by limiting chromosomal instability, DNA mutation, and inflammation while promoting immune surveillance, autophagic cell death, and senescence [112]. Reconciling these opposing functions, it was proposed that autophagy may play a critical role in suppressing tumors in the early stages of oncogenesis while sustaining the progression and the resistance of established tumors [112].

Variant discovery. Thirty-six genes throughout the entire autophagy pathway are associated with the risk, theragnostic, and clinical outcome of 30 different cancer types, regardless of the anatomical location or histological type (carcinoma, melanoma, sarcoma, and hematological malignancies) (Figure 4A). Without listing all 93 polymorphisms, we note that the *PIK3C3* SNPs tend to be enriched in different gastrointestinal cancers (esophageal [113,114], gastric [115,116],

colorectal [117], and pancreatic [118]). Likewise, variations of all members of the *ATG12* conjugation system (*ATG5, ATG7, ATG10, ATG12*, and *ATG16L1*) are associated with many solid cancer types (head and neck [119–121], breast [122–127], liver [78,128–130], bladder 131, and kidney cancers [132,133], and melanoma [134]), highlighting the pronounced impact of LC3 conversion in tumorigenesis (Figure 4B).

Beyond cancer risk, *ATG* SNPs emerge as universal predictors for a wide range of anti-tumor treatments as diverse as chemotherapy (anthracycline and/or taxane: *ATG5* [124]; cyclophosphamide: *ATG13* [139]; ASPG [asparaginase]: *ULK2* [140]; and platinum: *ULK1, ATG3, ATG14, ATG10, DRAM1* [141]), anti-angiogenic therapy (anti-VEGF: *RB1CC1* [142]), immunotherapy (BCG: *ATG2B, ATG5* [131]), targeted therapy (pazopanib: *ATG4A, ATG4C, ATG5* [132]; gefitinib: *ATG5, ATG7, ATG10, ATG16L2* [143]), and radiotherapy (*ATG10* [121]; *ATG12, ATG16L2* [144]; and *NBR1* [145]).

From genetics to biology. For patient management, the autophagy SNPs are confusingly protective or risk-enhancing. Located in non-coding genomic regions, these associations remain devoid of any molecular hypothesis. A few studies have so far documented a slight increase or decrease in ATG expression, but whether this is enough to have an impact on the autophagy flux remains elusive. Identifying the causal variants and understanding the underlying molecular mechanisms represent important challenges to clarify their contributions to tumorigenesis. We hope that the characterization of the cancer-associated *ATG* SNPs will help to estimate the cancer risk and guide the use of anti-cancer molecules.

D. Presumed guilty by association

Overall, by piecing together information from 243 studies, we observed that 67 *ATG* variants over the 263 are associated with several pairs of diseases; many are recognized comorbidities.

- Several are shared across *multiple inflammatory* or *autoimmune manifestations* that target the gastrointestinal tract, lung, heart, or multiple miscellaneous tissues: such as CD and asthma (*ULK1*, and *ATG12*), CD and rheumatoid arthritis (*IRGM, ATG5, ATG16L1*, and *ATG16L2*), CD and ankylosing spondylitis (*IRGM*), CD and cardiovascular diseases (*ATG4C, ATG4D*, and *ATG16L1*), CD and systemic lupus erythematosus (SLE; *IRGM, ATG5*, and *ATG16L2*), CD, SLE and Grave disease (*IRGM*) and asthma and SLE (*ATG5*), among others. This agrees with the co-occurrence of inflammatory and autoimmune diseases and the long-recognized roles of autophagy in immunity and inflammation [52, 132].
- Equally anticipated from the role of *inflammation* in *carcinogenesis*, a growing number of studies have highlighted the association of 13 *ATG* variants with one or more inflammatory diseases to one or more cancers: such as CD and NSCLC (*ULK1*), CD and cervical cancers (*ATG4A*), CD, asthma and cancers (*ATG5*), CD and gastric cancer glioma (*IRGM*), CD, arthritis and gastric cancer (*IRGM*), CD, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis and cancers (*ATG16L1*), CD, rheumatoid arthritis, SLE and NSCLC (*ATG16L2*), rheumatoid arthritis and multiple myeloma (*ATG5*), SLE and cancers (*ATG5*), and gastritis and gastric cancer (*CHMP2B*).
- Similarly, thirteen *ATG*s are associated with two to eight cancers (*ATG2B, ATG4A, ATG5, ATG7, ATG10, ATG12, ATG14, ATG16L1, ATG16L2, IRGM, MCL1, NBR1*, and *VMP1*), indicating extensive pleiotropy. It may seem also intuitive that *ATG* variations could predispose carriers to multiple independent primary cancers, a neglected hypothesis that deserves attention given the high morbidity of this malignancy. Along this line, mice with a mono-allelic deletion of *Becn1* show multi-site cancers (lymphoma, hepatocellular carcinoma and lung carcinoma) [135,136]. This was further supported by the deletion of *Ambra1* (liver and Lung cancers) [137] or *atg5* (osteosarcoma, hepatocellular carcinoma and lymphoma) [138] and the expression of the $Uvrag^{FS}$ mutant (colorectal carcinoma, and lymphomas) [99] (Figure 4C).
- Intriguingly, Pandora's box is also opened with *ATG* variants affecting 'apparently' unrelated phenotypes, such as degenerative diseases and cancer. For instance, several *ATG7* alleles are common to ccRCC and Parkinson disease. *ATG10* SNPs are a risk for breast cancer and Alzheimer disease, whereas *C9orf72* variants are related to prostate cancer and ALS-FTD, ALS, or schizophrenia. The same issue applies to cancers and cardiovascular diseases (*ATG9B, ATG7, ATG16L1*, and *ATG16L2*), (see for references **Tables S2-S7**).
- Even more remarkable is that 20 *ATG* SNPs across 6 autophagy genes (*IRGM, ATG4A, ATG5, ATG10, ATG16L1*, and *ATG16L2*) are associated with a *cluster of diseases* from autoimmune, inflammatory and infectious to degenerative diseases, and cancers. The most notable example is here again the *ATG16L1* T300A SNP that alone confers a pleiotropic systemic risk for 18 distinct illnesses. These include, beyond CD and the intestine boundaries, the following: cardiovascular [146], infectious [55,56,64,79], inflammatory diseases (COPD [147], rheumatoid arthritis [148], psoriasis [149], and Paget disease of bone [150]), and eight cancers (breast [126], head and neck [119], lung [151,152], thyroid [153], gastric [154,155], colorectal [156,157], and hepatocellular [129] cancers, and melanoma [134]).

From genetics to biology. Such a disease network agrees with the myriad of roles of autophagy in cancer, inflammation, infection, and neurodegeneration, thus pointing to an autophagy defect as the shared liability for these common diseases. However, caution is warranted when interpreting the data, because most arise from independent studies, and only three studies have associated an *ATG* SNP with two comorbidities in the same cohort (*ATG16L1*: HCC and cirrhosis [158], *IRGM*: Crohn disease and non-alcoholic fatty liver disease [159], and CD and arthritis [160]). Understanding such a high level of pleiotropy might be an important step towards developing new autophagy-modulating drugs that might benefit multiple conditions.

Translating *ATG* SNP pleiotropy into the clinic

A. Proof of principle and limitations of transgenic mice

In the quest for this demonstration, mouse models have been instrumental in establishing the liability of an autophagy

defect in cancer, neurodegenerative, inflammatory, autoimmune, and cardiovascular diseases [8]. A significant cornerstone is the demonstration in 2005 that the loss of autophagy in the central nervous system is sufficient to recapitulate the accumulation of aggregates and neurodegeneration in mice [10,11]. Thereafter, it was elegantly demonstrated that pharmacological activation of autophagy reduces, whereas inhibition of autophagy increases, the formation and the neurotoxicity of aggregate-prone aggregates (mutant HTT [huntingtin], mutant SNCA/α-synuclein, and mutant MAPT/tau [161–163]). Along these lines, the mono-allelic loss of several autophagy genes (*Atg16l1, Irgm1, Atg4c, Atg5, Becn1, Uvrag, Ambra1*, etc.) was demonstrated in mice to predispose to neurodegeneration, inflammatory disease, age-related cardiac injury, and cancer (see for references Figures 2C-**5C, S1C-S3C**).

Although these elegant preclinical models have undoubtedly linked defects in autophagy to pathologies, murine models do not sufficiently reflect the natural history of human diseases. The limitations include: *i*) essential differences between human and mouse physiologies, and hence, the functions of autophagy may be more or less different, and *ii*) deletions/loss-of-function *ATG* mutations performed in transgenic mice are not typical of common variations identified in complex human diseases (see **Tables S2-S7**). Far from the polygenic nature of human diseases, these mouse models explore the homozygous deletion of one gene with critical lethal phenotypes. Lastly, while pollutants and microbes are major environmental variables for human pathogenesis, laboratory mice are housed in highly controlled, sanitized, and ventilated cages. Only a few studies have emphasized the impact of tobacco and pathogens on the development of inflammatory diseases such as CD and COPD in *Atg16l1* [89,91], *egr1* [164], and *map1lc3b* [165] murine models. This difference severely limits the translation of findings from mouse models to the bedside of patients.

B. From the noise to risk threshold and polygenetic score

Fourteen years after the first GWAS on CD in 2007, 76 GWAS and 242 genetic studies later, we are still surprised to find a colossal gap between *ATG* SNP and disease risk correlations. The considerable investment and the subsequent information have not yet improved patient outcome, either for risk-stratification or response to therapy. The mutational landscape of autophagy can be viewed as an iceberg. The small visible portion of the iceberg, herein presented, represents the hotspots of missense, or frequently reported autophagy variations. In contrast, the larger and submerged portion of the iceberg is silent/non-coding mutations that have been overlooked, never reported, or insufficiently characterized.

Approximately 90% of the *ATG* SNPs are located in non-coding regions (Figure 5A). Given that these regions contain *regulatory* sequences (promoters, enhancers, introns, and 3′UTR), we assume that these non-coding variations may control mRNA abundance by influencing the *transcription, splicing*, and *stability* through binding of a transcription factor, splicing machinery, or microRNA. Therefore, any variation in these non-coding sequences might alter gene expression, affecting the autophagy flux, and disease susceptibility and severity.

One such example is the *IRGM* rs10065172 (c.313C>T), one of the most significant risk SNPs for CD. However, its discovery, a decade ago, has met some skepticism [166]. This was because this synonymous SNP does not change the sequence of the IRGM protein and was thus considered silent. Likewise, its high prevalence in 10% of unaffected populations argues against a pathogenic effect. Of interest, we showed that this type of synonymous SNP is of clinical relevance [167]. Indeed, this SNP changes the seed region of *MIR196*, a microRNA overexpressed in the inflamed intestinal epithelia of CD patients. Disrupting *IRGM* mRNA/miRNA regulation was sufficient to have an impact on IRGM expression and impair downstream clearance of bacteria by autophagy [167].

A few studies have reported the consequences of other non-coding *ATG* SNPs on the binding of upstream regulators, the activity of the promoters or 3′UTR by luciferase assays, and the downstream mRNA expression. Of interest, one of the biggest surprises to emerge from our analysis was that the variants linked to a disease tended to be active in the specific tissues that are relevant to this trait. To give the reader an overview of autophagic defects, we have thus completed the tables with the SNP annotations, the impact on transcription factor or miRNA binding, methylation, and expression quantitative trait loci (mQTL and eQTL) as much as possible from the literature or our analyses. We would like to encourage, through this review, collaborative effort to gain insight into the variant-regulator-phenotype 'trio' for an improved understanding of the regulation of the autophagy network that is linked to pathogenesis.

One hypothesis that emerges from these observations is that the rate of the autophagy flux is exquisitely sensitive to any change in the protein level of any autophagy member. Most *ATG* variants are non-coding and regulatory, with typically a *slight effect* on the level of *ATG* proteins. This infers that each *variant alone* is *not pathogenic*. As they do not interfere with the reproduction of their carriers, these SNPs escape negative selection. Some alleles such as $ATG16L1^{T300A}$ are even positively selected as they offer a selective advantage against some pathogens (*Mycobacterium ulcerans* [56], *S. typhimurium* [101], Uropathogenic *Escherichia coli* [64]) or tumor development (non-small cell lung cancers [151], thyroid cancer [153], colorectal cancer [156], and gastric cancer [168]). Likewise, given their high frequency, the co-occurrence of multi-allelic combinations is common in a large number of individuals.

Thus, we propose that: *i*) the synergy of all *ATG* alleles may become strong enough to reach a particular 'threshold' of susceptibility to the disease. *ii*) Exceeding such a risk threshold is dependent on multiple alleles, age, and exposure to an environmental factor. As a result, each variant alone has a *limited predictive* power, and when combined into a *polygenetic risk score*, the association may be more robust. With the increasing use of molecular profiling, we regret that there is no *autophagy gene panel-based testing* when identifying patients at risk for complex diseases. Although relevant for

a pathway, no study has brought together the effects of all *ATG* variants (*i.e.*, for the 69 autophagy members) into a polygenic risk score despite the importance it could have in estimating the risk, the genetic overlap between traits, and phenotype severity. Further studies are thus urgently needed to develop pan-autophagy polygenetic scores and validate their clinical utility in routine clinical practice.

C. The missing environmental link

The significant variability of disease expression by affected or unaffected 'healthy' carriers advocates for the intervention of environmental factors. Neither exposure to environmental challenges nor the presence of multiple genetic autophagy variants are individually the direct cause of a disease. Both combined genetic and environmental liabilities interact to push the individual over the threshold leading to disease. This notion presents considerable challenges and opportunities for the management of human diseases. We hope that understanding how autophagy gene-environment interactions affect disease outcome will guide more efficient and personalized treatment strategies. Limiting exposure to environmental factors or manipulating the host autophagy repair machinery should delay the onset of these diseases.

So far, the effects of *ATG* SNP-environment interactions have been primarily detected through the susceptibility to infection (Figure 5B). Likewise, approximately 15% of cancers are associated with hepatitis B virus (HBV), human papillomavirus, and *Helicobacter pylori*. While these infections are widespread, most infected people will not develop cancer. Of interest, people carrying variations in several autophagy genes have a greater risk of developing gastric (*H. pylori: ATG16L1* T300A [154,155], *IRGM* [155] and *CHMP2B* [169]), head and neck (HPV16 x smoking: *MCL1* [77]), hepatocellular (HBV: *ATG16L1* T300A [129], and *ATG5* [78,130]), and cervical (HPV: *ATG4A* [170]) cancers in response to infection.

As a point of entry, the lungs are constantly exposed to microbes, irritants, allergens, or pollutants (**Figure S1**). At play, autophagy is immediately upregulated to protect the host from these environmental insults. This might explain why the respiratory system is particularly vulnerable to a spectrum of alterations of autophagy in asthma (*ULK1* [171], *MAP1LC3B* [171], *ATG5* [171–174], *ATG7* [173] and *NUFIP1* [175]), pulmonary fibrosis (*ATG5, ATG10*, and *ATG12* [176], *TOLLIP* [177–179]), chronic obstructive pulmonary disease (COPD: *ATG16L1* [147], and *EGR1* [147,164]), tuberculosis (*ULK1* [65,66], *IRGM* [68–73], *ATG4C* [180], and *TOLLIP* [74–76]), and lung cancers (NSCLC: *ULK1, ATG3, ATG14, DRAM1* [141], *ATG4A* [181], *ATG5* 182, *ATG10* [141,151,183], *ATG12* [144,151], ATG16L1 [151], *ATG16L2* [144]; NSCLC *EGFR**: *ATG5, ATG7, ATG10, ATG12, ATG16L1, ATG16L2* [143]). Of global growing concern, COPD and lung cancers are the third most common cause of death and the leading cause of cancer-related death, respectively. Both result from chronic exposure to cigarette smoke and air pollution, a "silent killer" claiming five million lives worldwide every year (WHO, 2021 [2]). However, despite the magnitude of the health effects, only a few *ATG* variants have been associated with exposure to air pollutants, such as pulmonary fibrosis (coal: *ATG5, ATG10*, and *ATG12* [176]), asthma (diisocyanate: *NUFIP1* [175]), acute respiratory infections (AIR quality x rhinovirus: *TOLLIP* [81,82]), or lung cancer (non-smokers: *MCL1* [184]).

From genetics to biology. We acknowledge that the promising start to studies associating specific *ATG* SNPs with disease suffers from several limitations. So far, the *ATG* SNP-environment interactions remain elusive. From 243 studies (3.5 million participants), 52 studies (totaling 36,428 patients and 22,800 controls) have documented 'autophagy gene × environmental' interactions in conditions of infection (bacteria: 28 studies, 19,043 patients; virus: 9 studies, 2966 patients; and parasite: 2 studies, 950 patients), tobacco usage (7 studies, 11,772 patients), exposure to coal (1 study, 705 patients), bisphenol A (1 study, 200 patients), diisocyanate (1 study, 88 patients), and air pollution (3 studies, 854 patients). Of these studies, four were African, eight European, seven American, and twenty-six Asian. However, due to differences in allele frequencies, the predictive power of these findings in relation to European populations is limited. Thus, for future precision medicine we encourage new studies that broaden the ethnic diversity.

Attention should also be paid to gene regulation as most disease-associated SNPs are cis-eQTL, the expression of which is plastic and highly specific for a particular environmental cue. We now appreciate that pollutants are endocrine disrupters of signaling pathways and lead to abnormal gene expression. However, previous efforts have underestimated the impact of pollutants on the expression of *ATG* eQTL variants. Several arguments can be put forward to explain this huge gap: *i*) There is no assessment of the type of environmental exposure (external and internal levels, latency periods) in the investigated population-case cohorts. *ii*) Rather than a single-environment stress paradigm, it should be emphasized that we are exposed in the 'real world' to low but chronic exposure to a large variety of chemicals and stressors. Our modern lifestyle risk factors include pollutants, medication, pathogens, smoking, alcohol abuse, and diets rich in processed foods. *iii*) This intricate interaction is further complicated by the long latency period, with exposure to a causal agent typically occurring years to decades before disease diagnosis [185]. Thus, during our lifetime, our body accumulates long-lived and hydrophobic chemicals resulting from different routes and times of exposure. The totality of the pollutants and their metabolites in the blood and tissues is called the exposome [185,186]. *iv*) However, only a very limited number of widespread pollutants are currently monitored by the agencies that measure the quality of air, water, and food. As a result, it is challenging, if ever possible, to identify from 'short' monitoring the causal pollutants and stressors that affect the expression of *ATG* eQTL and thereby the onset of disease.

To tackle the complex mixture of contaminants, we propose to stimulate interdisciplinary research to develop, test, and validate internal and external biomarkers that could provide more accurate estimates of environmental exposure relevant to chronic environmental diseases. The impact of the environment on human health should then be reconstructed through a combination of blood-based autophagy polygenetic

and exposomics risk scores (i.e., we propose to call this the 'genexposomic' score). Identifying autophagy genexposomics biomarkers will provide both prevention programs to delay the onset of these devastating diseases in the at-risk population and the rationale of the manipulation of autophagy in new therapeutic opportunities.

Impact of autophagy SNP in the era of precision medicine: a place for autophagopathies

Taken together, the compilation of the *ATG* variations presented herein is a major step forward in understanding these common and untreatable diseases. However, as yet there are no clinical practice guidelines harnessing this genetic information, most likely because of the small effect of each variant. If these associations are confirmed, detecting the *ATG* risk alleles from blood samples will be critical for risk stratification, patient diagnosis, and treatment decisions. Such *ATG* SNP tests may identify CD patients with an increased risk of cancer, thus enabling diagnosis of cancer at an early stage when they have the best chance of being cured. This new information may also limit treatment choices, as immunosuppressive drugs for CD may further increase the risk of cancer. Although relatively rare, clinicians dealing with CD should also be aware of several *IRGM* SNPs linked to the increased risk of opportunistic tuberculosis. Similarly, we should remember that some *ATG* SNPs are associated with cancer and neurological diseases. Therefore, a critical challenge will be to recognize these *ATG* SNP carriers to help disease screening programs, prophylaxis, and precision care to promptly relieve complications of comorbidity. We thus propose the term '*autophagopathy*' to group together a class of genetic diseases the etiology of which concerns a defect in the autophagy machinery, whether directly related to an abnormal autophagic flux, LC3-associated phagocytosis, or any associated trafficking. This model assumes that neither genetic autophagy variants nor exposure to environmental challenges alone directly cause disease. However, SNPs that lead to low-autophagy impairment may alter the cell's ability to detoxify damaged organelles when challenged by an environmental factor. As a corollary, any *ATG* SNP would predispose individuals to develop this wide variety of diseases (such as cancer, infection, and neurodegenerative, cardiovascular, metabolic, and inflammatory diseases), only upon exposure to this particular environmental risk; the nature of which will determine the organ affected, and the diseases.

Thus, through this comprehensive atlas, we aim to bring autophagy into precision medicine. In the near future, physicians will offer patients the option to have their genome sequenced as a routine diagnostic procedure in their health care regimen. The autophagy-targeted SNP panel and the related polygenetic and exposomics risk scores will help predict an individual's risk of developing an autophagopathy. Because it will provide a diagnosis, and early treatment options, the implementation of this approach is a major global health issue.

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