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1 Review

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5 Selective Autophagy Receptors in Anti-Viral Defense.

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30

31 **Abstract:**

32 Autophagy ensures the degradation of cytosolic substrates by the lysosomal pathway.
33 Cargoes destined to be eliminated are confined within double-membrane vesicles called
34 autophagosomes, prior to fusion with endo-lysosomal vacuoles. Autophagy receptors
35 selectively interact with cargoes and route them to elongating autophagic membranes, a
36 process referred to as selective autophagy. Besides contributing to cell homeostasis,
37 selective autophagy constitutes an important cell-autonomous defense mechanism against
38 viruses. We review observations related to selective autophagy receptor engagement during
39 host cell responses to virus infection. We examine the distinct roles of autophagy receptors
40 in anti-viral autophagy, consider the strategies viruses have evolved to escape or oppose
41 such restrictions and delineate the contributions of selective autophagy to the tailoring of
42 anti-viral innate responses. Finally, we mention some open and emerging questions in the
43 field.

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55 **Keywords:** selective autophagy; autophagy receptors; viral infection; antiviral immunity, cell
56 autonomous defense.

57 **Autophagy and viruses**

58 **Autophagy** (see [Glossary](#)) is a major degradative pathway for the elimination of cytosolic
59 materials [1, 2, 3]. Autophagy regulates various cellular processes and defective autophagy
60 often translates into pathological situations [4]. The autophagic disposal of cytosolic
61 elements involves their encapsulation into a specialized double-membrane vesicle named
62 **autophagosome** that later brings the targeted material into contact with lysosomal
63 hydrolases upon fusion with late endosomes/lysosomes ([Box 1](#)). Autophagy is also an
64 important cell-intrinsic defense mechanism against cytosolic microbes especially viruses [5-
65 8]. Autophagy can interfere with the life cycle of viruses by opposing viral entry, altering
66 replication and virion egress through the degradation of viral components/particles and
67 modulating anti-viral immune response [9-14]. In response, viruses have evolved means to
68 resist, escape, or subvert the autophagic process. Unlike starvation-associated bulk
69 autophagy that randomly confines cytosolic portions, some forms of autophagy specifically
70 target particular **cargoes**. Such a process, referred to as **selective autophagy**, relies on the
71 engagement of cytosolic **autophagy receptors** that selectively bind to cargoes and direct
72 them to the autophagy machinery. Examples of autophagy receptors are **sequestosome-1**
73 **(SQSTM1)/p62** (p62), OPTN, NDP52, NBR1 and TAX1BP1 [15, 16] ([Box 2](#)). Cargo recognition
74 involves the interaction of dedicated regions of the receptor with the native cargo or with
75 biochemical tags conjugated to the cargo. For instance, ubiquitin that is conjugated to
76 cargoes through a three-step reaction resulting in single- or poly-**ubiquitination** [17, 18], is a
77 frequent tag sensed by autophagy receptors. Ubiquitin tags are recognized by **ubiquitin-**
78 **binding domains** (UBDs) present in autophagy receptors. The binding of galectins to newly
79 exposed carbohydrates on ruptured microbe-containing endocytic vacuoles is another signal
80 sensed by some autophagy receptors [8]. The connection of the targeted cargoes to the
81 autophagy machinery relies on the interaction of autophagy receptors with ATG8 family
82 factors (**LC3s and GABARAPs**) anchored on the developing **phagophore** [19, 20]. The
83 selective autophagic targeting of cytosolic microbes is referred to as **xenophagy** and in the
84 case of viruses, as **virophagy** [21, 22]. The relationship between autophagy and viruses at
85 large has been comprehensively reviewed [7, 22-27]. This review focuses specifically on the
86 roles of autophagy receptors during viral infection.

87

88 **Autophagy receptors in selective autophagy of viral components.**

89 Autophagic degradation of viral constituents or virions was observed for many viruses [7, 26,
90 28] and in some cases, the receptors involved were identified (Table 1). The spread of the
91 Sindbis virus (SINV), a positive strand RNA virus, is efficiently controlled by virus replication-
92 dependent autophagy [29]. In fact, in mice, autophagy protects the host from the lethal
93 infection of the central nervous system by clearing infection-associated aggregates that are
94 neurotoxic. p62 selectively interacts, in an ubiquitin-independent manner, with a protein of
95 the SINV capsid and promotes the autophagic degradation of the capsid [10]. The E3-
96 ubiquitin ligase SMAD-Ubiquitin Regulatory Factor 1 (SMURF1) is also involved in the capsid
97 protein degradation. SMURF1 interacts with the capsid independently of p62. SMURF1 does
98 not use its so-called homologous to the E6-AP carboxyl terminus (HECT) domain with E3
99 ubiquitin ligase activity, but instead, engages its C2 membrane-targeting domain, a domain
100 known to interact with membrane phospholipids [21]. Although the details of the C2 domain
101 -phospholipid interaction remain to be elucidated, it is clear that SMURF1 can mediate
102 selective cargo targeting and behave as an autophagy receptor-like factor. This response is
103 distinct from that occurring in *Mycobacterium tuberculosis*-infected macrophages where
104 SMURF1 engages both its HECT and C2 domains for selective autophagy of the bacteria
105 through the recruitment of the NBR1 receptor to subcellular structures that contain the
106 bacteria. In contrast, the recruitment of p62 to the same structures depends on the ubiquitin
107 ligase Parkin and not SMURF1 [30]. Besides SINV, SMURF1 also contributes to the autophagic
108 targeting of the double-stranded DNA Herpes simplex virus type 1 (HSV-1) lacking its ICP34.5
109 neurovirulence factor and thereby, undergoes autophagic degradation [21]. Hence, SMURF1
110 is a frequent player in autophagy receptor-mediated (i.e. selective) anti-viral autophagy.
111 Another mechanism contributing to p62 engagement during infection with SINV, HSV-1, and
112 with the double stranded DNA virus adenovirus (AdV), involves member 23 of the tripartite
113 motif (TRIM) family of proteins. TRIM factors comprise a Really Interesting New Gene (RING)
114 domain with E3 ubiquitin ligase activity, B box sequences and a coiled-coil domain. TRIM23
115 possesses an additional C-terminal ARF domain with GTPase activity. Upon infection, the
116 TRIM23 E3 ligase activity drives K27-linked polyubiquitination of its ARF domain, leading to
117 recruitment of the TANK-binding kinase 1 (TBK1). Subsequent dimerization and trans-
118 autophosphorylation of TBK1 results in p62 phosphorylation, a step that promotes p62-

119 mediated cargo-targeting [31]. Another factor that is able to interact with SINV and HSV-1
120 capsids to promote their autophagic degradation is the Fanconi anemia group C protein
121 (FANCC), a factor that also mediates mitophagy [32]. FANCC may function by directly
122 targeting capsids for autophagic degradation, although the mechanism involved is unknown.
123 Among the viruses mentioned above, some harbor a strong tropism for neuronal cells. As a
124 consequence, the interaction of autophagy receptors with viral components is likely to be
125 restricted to the nervous system of infected organisms.

126 Reminiscent of its role in SINV infection, p62 also binds to the capsid of another positive
127 sense RNA virus of the Togaviridae family, namely the Chikungunya alphavirus (CHIKV) to
128 mediate capsid degradation, leading to attenuated replication and cell death since capsid
129 accumulation is cytotoxic [33]. To bind to CHIKV capsid, p62 interacts with ubiquitinated
130 tags. Unlike during SINV infection, SMURF1 did not appear to co-localize with p62. NDP52,
131 yet another autophagy receptor, also contributes to cytoprotection by interacting with the
132 CHIKV nonstructural protein nsP2, a multifunctional enzyme important for viral replication,
133 causing its cytosolic retention and limiting the nuclear cytotoxicity of nsP2. However, unlike
134 p62 that attenuates CHIKV replication, NDP52 promotes the activity of CHIKV replicative
135 complexes due to nsP2 accumulation near the trans-Golgi network [33]. Thus, during
136 infection, p62 and NDP52 play distinct roles that nevertheless tend to ultimately benefit to
137 CHIKV as both contribute to host-cell survival. Possibly, p62 could also mediate the
138 autophagic degradation of the VP1 capsid protein of the picornavirus Foot-and-Mouth
139 Disease Virus (FMDV) as many developing autophagosomes display a LC3-p62-VP1
140 colocalization. However, a direct p62-VP1 interaction remains to be documented [34].

141 In epithelial cells, the attenuated form of the measles virus (MeV), a morbillivirus of the
142 Paramyxoviridae family, triggers ordered phases of autophagy [35]. The first phase depends
143 on the MeV receptor, CD46 whose Cyt-1 isoform activates the class III PI3K complex I, a
144 complex that is instrumental for phagophore elongation ([Box 1](#)), via a scaffold protein called
145 GOPC [36]. Whether autophagy receptors are significantly engaged in this early autophagy
146 remains to be studied. Another phase of autophagy occurs later due to interaction of the
147 viral C protein (MeV-C) with an innate immunity enzyme named Immunity-Related GTPase
148 family M (IRGM) [37].

149 Other MeV proteins known to mediate cell-cell fusion (MeV H and F), further promote
150 autophagy and viral replication through the sustained formation of syncytia [35, 38]. In
151 contrast to OPTN that has no effect, p62 appears to exert a negative control on MeV
152 replication [39]. Although p62 can interact with the MeV nucleoprotein (N) [37], whether
153 MeV-N is targeted by p62 for autophagic degradation is unknown.

154 Among TRIM factors, TRIM5 α promotes autophagy by interacting with the core autophagy
155 factor Beclin 1 (see Box 1). In addition, it can also behave as a selective autophagy receptor
156 by interacting with ATG8 factors and the human immunodeficiency virus 1 (HIV-1) capsid
157 factor p24. Such interactions direct p24 to autophagosomes in cooperation with p62 while
158 triggering autophagy in a ULK1-Beclin 1-dependent fashion [40]. In order to resist natural
159 immune response, HIV-1 induces proteasomal degradation of the anti-viral editing enzyme
160 APOBEC3G through the HIV-1 factor Vif that promotes the ubiquitination of APOBEC3G [41].
161 At the same time, the host factor histone deacetylase-6 (HDAC6) engages its ubiquitin zinc
162 finger (BUZ) domain to bind APOBEC3G and causes Vif degradation by autophagy, helping
163 host cells to limit HIV-1 replication [42]. In CD4 T lymphocytes, autophagy selectively
164 degrades the HIV-1 factor Tat that interacts with p62 in a ubiquitin-independent manner
165 [43]. In Langerhans cells, the targeting of langerin-associated HIV-1 to autophagic
166 degradation depends on TRIM5 α that promotes the formation of autophagy-inducing
167 complexes [44]. Thus, TRIM5 α can act as an autophagic receptor that is capable of binding
168 retroviral capsid components without the need for cargo ubiquitination and alongside more
169 classical autophagy receptors, contribute to restrict HIV-1 infection. Besides HIV-1 infection,
170 TRIM5 α is also involved in autophagy associated with HSV-1 infection although an
171 autophagy receptor-like role was not studied [31].

172 With respect to p62, it is worth noting that in *Drosophila melanogaster*, the p62 orthologue
173 (Ref(2)P) contributes to resistance to the sigma rhabdovirus with a prominent role for its PB1
174 domain [45]. As Ref(2)P co-localizes to aggregates induced upon attenuated autophagy [46],
175 it may operate as a bona fide selective autophagy receptor capable of contributing to the
176 restriction of the sigma virus and hypothetically, the vesicular stomatitis virus (VSV) [9].
177 Ref(2)P is also involved in the autophagic restriction of the flavivirus Zika virus in the adult
178 *Drosophila* brain [47]. This observation, along with other observations related to

179 alphaviruses, suggests that the capacity of selective autophagy to oppose arboviral infections
180 is conserved between mammals and flies. The targeting of virus determinants by autophagy
181 receptors could be observed in even more distant organisms. In *Arabidopsis thaliana*, NBR1
182 targets both the soluble capsid protein P4 and assembled capsids of the pararetrovirus
183 cauliflower mosaic virus (CaMV) for autophagic degradation. Interestingly, the NBR1-P4
184 interaction seems ubiquitin-independent [48]. Hence, the contribution of autophagy to cell-
185 intrinsic defense against viruses appears conserved among highly distant organisms ([Figure](#)
186 [1, Key Figure](#)).

187

188 **Viral strategies to counteract autophagy receptor engagement and escape selective** 189 **autophagy.**

190 *Cleavage of selective autophagy receptors.*

191 One of the strategies that viruses have evolved to resist autophagic degradation involves the
192 cleavage of autophagy receptors by viral proteases. The picornavirus, coxsackievirus B3
193 (CVB3) uses its 2A protease to cleave p62 [49, 50]. In addition, CVB3 proteases 2A and 3C
194 can cleave NBR1, while 3C can also cleave NDP52 [50, 51]. Thus, both p62 and NDP52 that
195 are known to target ubiquitinated VP1 capsid component of CVB3 for degradation [51], are
196 cleaved by CVB3 proteases. Interestingly, the 3C-cleaved form of NDP52 can still target the
197 antiviral signaling protein MAVS for degradation, leading to attenuated **type I interferon**
198 (IFN-I) response [50]. Importantly, cleaved forms of p62 and NBR1 are dominant negative
199 factors relative to their native counterparts [51]. Enterovirus D68 (EV-D68), rhinovirus 1A
200 (RV1A) and poliovirus 1 (PV) are other enteroviruses with proteases that are able to cleave
201 p62 [52]. Among Flaviviruses, both Dengue (DENV) and Zika (ZIKV) viruses use the NS3-NS2B
202 viral complex to cleave FAM134B, an important receptor for endoplasmic reticulum (ER)-
203 phagy [53]. FAM134B silencing augments DENV/ZIKV replication pointing to an anti-viral role
204 possibly through FAM134B-mediated targeting of viral NS3 since a cleavage-resistant form of
205 FAM134B increases FAM134B-NS3 co-localization [53]. p62 may also contribute to anti-
206 DENV autophagy as p62 overexpression reduces the production of viral particles [54]. Taken
207 together, the observations relative to the degradation of autophagy receptors by particular

208 viral proteases strongly support the notion that virus-autophagy receptor interaction can be
209 instrumental to control viral infection.

210

211 *Targeting of selective autophagy receptor regulators.*

212 As evoked above, HSV-1 uses the ICP34.5 factor to resist autophagy. Besides the interaction
213 of ICP34.5 with Beclin 1 resulting in attenuation of autophagy [55, 56] and inhibition of the
214 anti-viral protein kinase R (PKR) [57], ICP34.5 inhibits the regulatory activity exerted by TBK1
215 [58] on p62, OPTN, NDP52 and TAX1BP1. For instance, TBK1 phosphorylates both the LIR and
216 UBD domains of OPTN and p62 leading to them showing increased affinity for their cargoes
217 [59]. Thus by inhibiting TBK1, ICP34.5 perturbs the functions of multiple autophagy
218 receptors.

219

220 *Alteration of selective autophagy via recruitment of host cell factors.*

221 Recruitment of host cells factors can also interfere with selective targeting. For instance,
222 after endocytosis, the AdV capsid exposes the membrane lytic protein VI (PVI) to rupture the
223 endosome and allow AdV to access the cytosol. This step requires the interaction of a
224 conserved PVI motif (PPxY) with the HECT E3 ubiquitin ligase Nedd4.1/.2. When AdV lacks
225 the PPxY motif, PVI is still endosomolytic but the virus exit from the endosome is poor due to
226 autophagosome formation. Such an autophagosome biogenesis appears initiated by the
227 engagement of host lectines (Galectin-3, -8 and -9) that sense newly exposed β -galactosides
228 on the ruptured endosomal membrane. Autophagy inhibition or Galectin-8 (but not -3/-9)
229 depletion both restore the capacity of PPxY-deficient AdV to reach the cytosol, indicating a
230 Galectin-8-dependent autophagic restriction of the mutant virus [12]. p62 and NDP52 are
231 detected at the endocytic membrane rupture site but are not required for autophagic
232 degradation of the mutant virus, suggesting that other receptor(s) are involved. Of these, a
233 possible candidate is TAX1BP1 as it can bind Galectin-8. Other candidates include TRIM
234 family factor(s). Besides the fact that TRIM5 α can behave as a receptors, some TRIM factors
235 cooperate with Galectins to promote selective autophagy in situ via recruitment of upstream
236 autophagy factors such as Beclin 1 or ULK1 in response to endosome rupture [60, 61]. How

237 the PPxY-Nedd4.1/.2 interaction permit AdV to escape Galectin-8-dependent autophagy
238 remains unknown. Coxsackievirus B1 and poliovirus are picornaviruses that also recruit host
239 cell factors to resist autophagic responses when transferring their RNA from punctured
240 endosomes into the cytosol. This requires recruitment of the lipid modifying factor PLA2G16
241 at the rupture site, leading to altered Galectin 8-dependent autophagy [62]. With respect to
242 NDP52, it is known that it can be recruited to bacteria-containing endosomes by the small
243 guanosine triphosphatase Rab35 to promote their autophagic degradation [63]. Whether
244 Rab35 is also involved in the selective autophagy of virus-containing endosomes remains to
245 be examined.

246

247 **Exploitation of autophagy receptor functions by viruses to take advantage of selective** 248 **autophagy.**

249 Viruses can also take advantage of the host cell autophagy machinery. Viruses such as MeV
250 benefit from the autophagy flux for optimal replication. Unlike p62, that diminishes
251 replication, NDP52 and TAX1BP1 promote MeV replication [39]. Indeed, NDP52, TAX1BP1
252 and OPTN, but not p62, not only mediate cargo targeting but also positively regulate
253 autophagosome maturation. This role involves both dedicated LIR-motifs and a motif that
254 connects autophagosomes to the endo-lysosomal machinery through the binding of the
255 motor protein Myosin VI [39, 64, 65]. Thus, MeV takes individual advantage of the pro-
256 maturation role of at least two autophagy receptors to favor its replication. This could be the
257 result of the direct interaction of MeV-N with TAX1BP1 and MeV-C/V with NDP52 [39].
258 Possibly, other paramyxoviruses which interact with the autophagy machinery very similarly
259 to MeV [66] could benefit from the same effect.

260

261 **Role of autophagy receptors in calibration of innate responses to viral infections.**

262 *Infection-related induction of selective autophagy.*

263 Upon viral nucleic acid sensing, pattern recognition receptors such as TLRs, RLRs and other
264 sensors activate critical signaling pathways for the defense of the host, including NF- κ B and
265 IFN-I pathways [67, 68] (Box 3). Through cognate receptors, secreted IFN-I activate the

266 expression of multiple IFN-stimulated genes that mediate anti-viral defense [69, 70]. As for
267 many anti-microbial effectors, IFN-I production must be regulated to avoid deleterious
268 effects on host tissues [71, 72]. To this respect, NDP52 mediates the degradation of MAVS by
269 ubiquitin-dependent selective autophagy during VSV and Sendai virus (SeV) infections [73].
270 Among factors autocrinally induced by IFN-I is Tetherin (also named BST2 or CD137), a factor
271 that recruits the E3 ubiquitin ligase MARCH8 for K27-linked ubiquitination of MAVS and its
272 autophagic degradation mediated by NDP52. Thus, an NDP52-dependent autophagic
273 feedback loop regulates virus-induced IFN-I to prevent excessive IFN-I production [73].
274 Opportunistically, viruses may enforce such retro-circuits to further soften IFN-I response.
275 VSV thus increases expression of the cytosolic E3 ubiquitin ligase RNF34 that further
276 branches K27-linked chains on MAVS increasing its targeting by NDP52 for degradation
277 through mitophagy [74]. Hence, VSV dampens IFN-I production by manipulating the capacity
278 of NDP52-mediated mitophagy to regulate MAVS level. The virus also affects NF- κ B
279 activation through MAVS [75]. Unlike NDP52, p62 was not involved in selective autophagy
280 of MAVS during SeV or VSV infection. However, p62-mediated autophagy can also attenuate
281 virus-induced IFN-I production. SeV and VSV infection induce the IFN-I-inducible factor ISG15
282 that interacts with RIG-I allowing it to interact with the Leucine-rich repeat-containing
283 protein 25 (LRRC25) to form a complex where RIG-I becomes recognizable by p62 and is
284 subjected to autophagic disposal to regulate IFN-I production [76]. In turn, such a negative
285 control of RIG-I by selective autophagy is itself balanced by the fact that under conditions of
286 SeV infection, the LRRC59 factor interacts with ISG15-associated RIG-I leading to competition
287 with LRRC25 and attenuation of p62-mediated RIG-I targeting [77]. In cells infected with SeV,
288 VSV and encephalomyocarditis virus (EMCV), the newly exposed CARD domain of RIG-I
289 undergoes K63-linked poly-ubiquitination. At the same time, infection induces the coiled-coil
290 domain-containing protein 50 (CCDC50) that interacts with both K63-ubiquitinated RIG-I and
291 LC3 on phagophores leading to autophagic degradation of RIG-I. Thus, CCDC50 somehow
292 functions as an autophagy receptor to attenuate IFN-I response [78]. TLR3 uses the adaptor
293 TRIF for downstream signaling upon sensing of dsRNA of viral origin. Excessive TRIF
294 engagement can be controlled via the TRIM32 host factor that interacts with both TRIF and
295 the TAX1BP1 receptor to selectively target TRIF for degradation and results in attenuation of

296 TLR3-associated immune responses [79]. NDP52 can also mediate selective autophagy of
297 TRIF and TRAF6 leading to attenuated NF- κ B activation in the case of TRAF6 [80].

298

299 *Modulation of constitutive selective autophagy during infection.*

300 Virus sensors are also targetable by selective autophagy at steady state and infection-related
301 IFN-I production can modulate this targeting to adjust host cell responses. cGAS is an
302 important sensor of microbial dsDNA that activates IFN-I signaling via cGAMP-mediated
303 activation of STING and mobilization of IRF3. At steady state, the sensing of K48-linked
304 ubiquitin chains on cGAS by p62 targets cGAS for autophagic degradation to regulate basal
305 cGAS level. During HSV-1 infection, IFN-I activates the expression of TRIM14 that interacts
306 with cGAS and recruits the deubiquitinating factor USP14 to hydrolyze K48-linked ubiquitin
307 chains allowing cGAS to escape p62-mediated degradation [81]. Thus, cGAS is constitutively
308 controlled by p62-dependent autophagy and infection-induced TRIM14 consolidates
309 activation of IFN-I signaling by attenuating this autophagy. The interaction of HSV-1 DNA
310 with cGAS allows cGAS to bind the Beclin 1 complex, an interaction that prevents excessive
311 IFN-I production by diminishing cGAMP production. Another consequence of HSV-1-induced
312 cGAS-Beclin 1 interaction is the dissociation of a negative regulator called Rubicon from the
313 Beclin 1 complex, leading to an enhanced autophagic response that also degrades HSV-1
314 DNA [82]. Autophagy receptors involved in this targeting remain to be identified. At steady
315 state, p62 also mediates the autophagic degradation of MAVS once coupled with an iron
316 metabolism-related factor called HFE. Infection with SeV or VSV suppresses HFE expression
317 and promote virus-triggered IFN-I production due to improved MAVS stability [83]. Thus,
318 during viral infection, changes in the steady state control of IFN-I pathway factors by
319 selective autophagy can be restrictive for the virus. As for cytosolic IRF3, it is subject to
320 constitutive K27-linked polyubiquitination leading to NDP52 recognition and autophagic
321 degradation. Such degradation is equilibrated by the deubiquitinase PSMD14 (also named
322 POH1 or Rpn11) that removes K27-linked ubiquitin chains thereby ensuring a stable pool of
323 IRF3 at steady state. Upon SeV infection, PSMD14 gets dissociated from IRF3, facilitating K27-
324 linked polyubiquitination and increasing IRF3 degradation. In addition, virus-induced IFNs
325 promote the expression of the E3 ligase TRIM21 that enhances K27-linked polyubiquitination

326 of IRF3 further favoring its autophagic control [84]. How infection translates into dissociation
327 of the IRF3-PSMD14 complex is not understood. It is also unknown whether NDP52
328 contributes to another autophagic circuit that can negatively regulate the level of IRF3 in
329 SeV-infected cells. This circuit comprises of the IFN-I-inducible factor IFITM3, which binds to
330 IRF3, thereby making it susceptible to autophagic degradation and attenuating IFN-I
331 production [85]. Besides modulating ubiquitination of IRF3, TRIM21 could behave as an
332 autophagy receptor as it can directly bind to both IRF3 dimers and ATG8 factors and also
333 recruits the core autophagy factors, Beclin 1 and ULK1. A role for p62 in autophagic
334 degradation remains plausible as TRIM21 can also bind to p62 [86]. These situations ([Table](#)
335 [2](#)) illustrate how selective autophagy can regulate the homeostasis of antiviral pathways at
336 steady state and how such a regulation can be modified in various ways during viral infection
337 ([Figure 1](#)).

338

339 **A selective autophagy receptor-like role for viral factors.**

340 The Hantaan virus (HTNV) manipulates autophagy to attenuate innate responses. By binding
341 to the Tu Translation Elongation Factor Mitochondrial (TUFM), causing mitochondrial
342 damages and interacting with LC3B, HTNV glycoprotein (Gn) promotes accelerated
343 mitophagy that diminishes the pool of MAVS and reduces the capacity to produce IFN-I [87].
344 Thus, by functioning as an autophagy receptor, HTNV Gn rapidly dampens IFN-I responses
345 through mitophagy-associated MAVS degradation, meaning that the receptor is degraded at
346 the same pace as the cargo. Therefore, Gn-mediated mitophagy leads to degradation of Gn.
347 HTNV subsequently hinders this mitophagy to ensure particle production: later during
348 infection, the nucleocapsid protein (NP) interferes with the Gn-LC3B interaction by binding
349 to LC3B and alters autophagosome-lysosome fusion by binding to the maturation permissive
350 factor SNAP29 ([see Box 1](#)). Whether the capacity of Gn to behave as an autophagy receptor
351 is a particularity of HTNV or whether it is a common trait among Bunyaviruses is unknown.
352 The case of HTNV is somehow reminiscent of that of the human parainfluenza virus type 3
353 (HPIV3) member of the Paramyxoviridae family. In this instance, the viral matrix protein (M)
354 interacts with both TUFM and LC3 and acts as an autophagy receptor to drive mitophagy and
355 attenuate IFN-I production [88]. The protein M translocates into the mitochondria and upon

356 ubiquitination, binds efficiently to LC3. Over-consumption of the M protein is re-equilibrated
357 by the viral phosphoprotein P that inhibits autophagosome maturation through interaction
358 with SNAP29 [89]. The targeting of the mitochondria by viral factors is not rare. For instance,
359 the influenza A virus protein PB1-F2 attenuates IFN-I production by translocating into
360 mitochondria and reducing the inner membrane potential, ultimately causing mitophagy
361 [90]. It would be interesting to estimate how often viral factors can behave as *bona fide*
362 autophagy receptors.

363

364 **The issue of autophagosome formation at the site of autophagy receptor engagement**
365 **during viral infection.**

366 Besides selectively targeting cargoes for encapsulation into autophagosomes, autophagy
367 receptors can trigger phagophore formation in situ by recruiting factors involved in the early
368 steps of autophagy. In yeast, cargo targeting by the Atg19 receptor can activate the Atg1
369 kinase complex (homologous to the mammalian ULK1 complex) through interaction with the
370 scaffold factor Atg11. Atg1 kinase complex clustering promotes its auto-phosphorylation and
371 autophagic membrane formation [91-93]. In mammals, NDP52 and OPTN receptors can
372 stimulate phagophore formation through ULK1 recruitment during mitophagy [94].
373 Phagophore induction is also initiated when NDP52 senses Galectin-8 adsorbed onto
374 damaged *Salmonella*-containing vacuoles and recruits both ULK1 and TBK1 kinase complexes
375 via interaction with FIP200 and adaptors of TBK1 [95]. In-situ induction of autophagic
376 membranes can also occur upon sensing of ubiquitinated mitochondria and peroxisomes by
377 NDP52 [96]. As for p62, it recruits FIP200 (via a domain of FIP200 that has homology with
378 yeast Atg11) to p62-associated aggregates of ubiquitinated proteins for their autophagic
379 degradation. Hence, NDP52-mediated recognition of either ubiquitinated viral components
380 or Galectin-8 decorated, virus-containing endosomes, could locally recruit ULK1 and TBK1
381 kinase complexes for in-situ phagophore induction during virus infection. Because p62 and
382 TAX1BP1 both have the capacity to interact with FIP200, they are additional candidates for in
383 situ recruitment of ULK1 and phagophore induction in virus-infected cells.

384

385 **Concluding remarks**

386 As emphasized elsewhere [26], the observation that virions could be found in the vicinity of,
387 or confined within, double-membrane vesicles in infected cells is ancient [97]. The
388 comprehension that this phenomenon reflects an active anti-viral autophagic resistance and
389 that this resistance can be selective is, in contrast, recent [5, 28, 98]. Among selective
390 autophagy receptors that target various types of viruses, p62 is frequent and its role appears
391 conserved in, at least, some invertebrates. However, whether it constitutes a master
392 receptor for anti-viral selective autophagy is unclear. Nearly thirty mammalian factors have
393 been identified with selective autophagy receptor functions [16]. Numerous receptors were
394 also found in yeast, suggesting that a large panel of such receptors may be general to both
395 yeast and metazoans. To which extent anti-viral selective autophagy takes advantage of such
396 diversity and how diverse is the set of viral factors that are targetable by autophagy
397 receptors remain to be delineated ([see Outstanding Questions](#)). In turn, viruses can oppose
398 selective autophagy by cleaving autophagy receptors, interfering with upstream factors that
399 regulate receptors or recruiting endogenous factors that compromise receptor engagement.
400 Autophagy is activated in many viral infections [7, 26, 28]. Yet, the role of autophagy
401 receptors in such mobilization is rarely known. For instance, autophagy contributes to the
402 presentation of viral antigens by major histocompatibility complex molecules to cognate T
403 lymphocytes [99] but the autophagy receptors involved in this process are unknown.
404 Autophagy receptors also contribute to both constitutive and infection-related calibration of
405 IFN-I-inducing pathways by mediating selective autophagic degradation of major
406 sensors/regulators of such pathways. Whether autophagy receptors engaged in antiviral
407 selective autophagy can also promote in situ phagophore formation is an important issue to
408 be addressed. Future research should provide insights into these questions and improve our
409 understanding of both the viral strategies used to optimize replication and the functioning of
410 highly selective forms of autophagy.

411

412

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418 space limitation.

419

420 **Box 1. An overview of the mammalian autophagy process.**

421 The autophagy machinery includes dozens of autophagy proteins (ATGs) [2] controlled by
422 three major complexes. The ULK1 kinase complex (including Unc-51-like kinase 1 (ULK1) and
423 FAK family kinase-interacting protein of 200 KDa (FIP200)), the Class III phosphoinositide 3-
424 kinase (PI3K) complex I (including Beclin 1) and the ATG5—ATG12-ATG16L1 complex [100].
425 Events that induce autophagy activate the ULK1 complex that itself activates the Class III
426 PI3K complex I, leading to generation of phosphatidylinositol-3-phosphate (PtdIns3P)-
427 enriched micro-domains on the endoplasmic reticulum (ER) or other membranes. This step
428 represents the initiation phase of autophagy. The initiation membrane becomes a cup-
429 shaped structure called the phagophore that is the precursor of the future autophagosome.
430 ATG8 factors (ATG8s-I) are soluble proteins that are subjected to conjugation with
431 phosphatidylethanolamine (ATG8-II) for insertion into the phagophore, a phase called
432 elongation. In mammals, ATG8s include microtubule-associated protein light chain 3
433 (MAP1LC3/LC3) A-C and γ -aminobutyric acid receptor-associated protein (GABARAP) L1-3
434 [19]. ATG8 factors are the anchoring point for autophagy receptors that route cargoes to the
435 phagophore. This interaction involves motifs named ATG8-interacting motifs (AIMs) (LC3-
436 interacting regions (LIRs) and GABARAP-interacting motif (GIM) for LC3s and GABARAPs,
437 respectively). Once formed, autophagosomes recruit several factors important for the fusion
438 of autophagosomes with late endosomes-lysosomes. Among those are N-acetylmaleimide-
439 sensitive factor attachment protein receptors (SNAREs) syntaxin 17 (STX17) and YKT6, the
440 SNARE SNAP29, and vesicle-associated membrane protein 8 (VAMP8). The STX17-SNAP29-
441 VAMP8 tri-molecular interaction is central to this fusion that generates autolysosomes
442 where cargo degradation occurs [3]. This step called autophagosome maturation is catalyzed
443 by the Class III PI3K complex II in which Beclin 1 also plays a role [3]. The initiation-
444 elongation-maturation sequence constitutes the autophagy flux.

445

446 **Box 2. Selective autophagy receptors.**

447 Sequestosome-1 (SQSTM1)/p62 (p62) is the prototypic autophagy receptor. Its N-terminal
448 PB1 region optimizes its function through oligomerization, and the C terminus contains the
449 UBD (UBA). In between, p62 possesses several protein-protein-interaction regions: a Zinc

450 finger domain (ZZ), a TRAF6-binding domain and a region interacting with the E3 ligase
451 Keap1 (KIR). The ATG8 factor binding motif (AIM) is upstream of the KIR domain. Next to
452 BRCA1 gene 1 protein (NBR1) is another receptor with homology to p62. It dimerizes via its
453 coiled-coil domain and also oligomerizes with p62 via its PB1 domain. p62 and NBR1 can
454 cooperate to mediate aggrephagy. Identified in the context of *Salmonella* infection, the
455 nuclear dot protein 52 kDa (NDP52/CALCOCO2) recognizes ubiquitinated bacteria via its C-
456 terminal Zinc finger domain (UBZ) and direct them to autophagic degradation by engaging a
457 non-canonical AIM. On the C terminus, sequence elements that bind Myosin 6 are important
458 for the overall functioning of NDP52 although not crucial for the cargo-targeting function.
459 The N-terminal SKIP carboxyl homology (SKICH) domain is important for the receptor
460 function in both xenophagy and mitophagy. NDP52 dimerizes via its coiled-coil domain.
461 Related to NDP52 is Tax1-binding protein 1 (TAX1BP1/T6BP) also able to target ubiquitinated
462 *Salmonella*. It differs from NDP52 by a higher number of coiled-coil domains. Both NDP52
463 and TAX1BP1 use their SKICH domain to interact with the adaptor NAP1 to associate with
464 TBK1, an important regulatory partner that phosphorylates several Ser/Thr residues.
465 However, unique to NDP52 is the capacity to bind Galectin 8 through a galectin-interacting
466 region (GIR) upstream of the UBZ. Besides NDP52 and TAX1BP1, the capacity to bind Myosin
467 6 is shared by the optineurin (OPTN) receptor. OPTN is rich in coiled-coil region, undergo
468 oligomerization and also depends on TBK1, in particular for its robust interaction with LC3B.
469 Of note, oligomerization/dimerization is a common feature of autophagy receptor, most
470 likely because it increases the density of AIMS in situ. Importantly, the recognition of
471 ubiquitin tags is not an absolute requirement for cargo targeting as some receptors operate
472 without it. NIX/BNIP3L, BNIP3 and PHB2 that mediate mitophagy, are examples of such
473 ubiquitin-independent receptors. A growing number of autophagy receptors involved in
474 selective autophagy is being identified, especially in mammals [15, 16].

475

476 **Box 3. Signaling in the IFN-I anti-viral innate immune response.**

477 Hosts cells respond to viral infection by secreting IFN-I that opposes viral replication,
478 promotes death of infected cells and favor subsequent immune responses. Viral infections
479 can be sensed through Toll-like receptors (TLRs), RIG-I-like receptors (RLRs) such as the

480 cytosolic RNA helicase detectors MDA-5 and RIG-I/DDX58 (RIG-I) or sensors such as the
481 cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS) [67, 68]. In all cases, the sensing
482 leads to activation of interferon regulatory factor (IRF) and NF- κ B transcription factors
483 supporting the expression of IFN-I (that in turn triggers the production of multiple antiviral
484 effectors through binding to IFN-I receptors) and pro-inflammatory cytokines. At the level of
485 intracellular membranes, TLR3/7/8/9 react to viral nucleic acids at the endosomal level upon
486 endocytosis or during replication. TLR3 senses double strand RNA and through recruitment
487 of TRIF and TRAF3/6, PI3K and T47AB-TAK1-RIP1 complex ultimately activates IRF3, AP1 and
488 NF- κ B. TLR7/8 and TLR9 detect single strand RNA and nonmethylated CpG DNA respectively
489 and, through MyD88, IRAK, TRAFs and IKK α , lead to activation of IRF7. Although TLR4
490 induces proinflammatory cytokines and IRF3-dependent IFN-I in response to gram-negative
491 bacteria, it can also react to some glycoproteins from viruses such as VSV. Within the
492 cytosol, negative-strand viral RNAs are detected by RIG-I while their positive counterparts
493 are sensed by MDA-5. In both cases, the sensing leads to exposure of CARD domains able to
494 mediate interaction with the MAVS/IPS-1/Cardif/VISA adaptor present on mitochondrial
495 outer membrane, a process enhanced by TRIM25 dependent polyubiquitination. MAVS
496 then interacts with adaptors including TRAF3/6 and kinase complexes such as IKK $\alpha\beta\gamma$, TANK-
497 TBK1-NAP1-IKK ϵ or TAK1-TAB that activate IRFs, AP1 and NF- κ B for gene expression. IRF3
498 reaches the nucleus after TBK1-mediated, phosphorylation-dependent dimerization and
499 induces IFN-I. Cytosolic viral DNA can be sensed by cGAS that dimerizes and synthesizes a
500 second messenger called cyclic GMP AMP (cGAMP). cGAMP activates a protein of the
501 endoplasmic reticulum named stimulator of interferon genes protein (STING) that recruits
502 several kinases including TBK1 to activate IRF3 for IFN-I induction, MAP3K14/NIK that
503 mobilizes non-canonical NF- κ B signaling, and I κ B kinase (IKK) that triggers canonical NF- κ B
504 signaling.

505

506 **Legend to Figure 1, Key figure. Selective autophagy in antiviral defense.**

507 During various viral infections, autophagy receptors can sense ruptured virus-containing
508 endosomes, viral proteins or assembled viral capsids for targeting to developing
509 phagophores, encapsulation into autophagosomes (AP) and degradation in autolysosomes

510 (AL) upon autophagosome fusion with lysosomes (LYS). Antiviral autophagy can thus
511 interfere with both viral entry and viral replication/egress. Autophagy receptors interact
512 with phagophore-anchored ATG8 factors by using dedicated motifs (AIMs). Other domains of
513 autophagy receptors are specialized in the interaction with Galectin-8 on ruptured
514 endosomes, with ubiquitinated viral proteins (ubiquitin binding domains) or with native viral
515 components (protein-protein interactions domains). Concomitantly, selective autophagy is
516 also involved in modulating/adjusting the capacity of cells to produce type I interferon (IFN-I)
517 during viral infection. In such case, autophagy receptors can target sensors (S) and adaptors
518 involved in viral nucleic acid sensing (TLRs, cGAS, RIG-I, MAVS, TRIF) and transcription factors
519 (TF) involved in virus-induced IFN-I production (e.g. IRF3). Again, such a targeting may
520 involve recognition of ubiquitin tags on the targeted factors. Virus can interfere with anti-
521 viral functions of autophagy receptors through various molecular strategies (listed in red).
522 The dashed grey arrow indicates that intermediate events of vesicle-vesicle fusion are not
523 represented. Targeting interactions mediated by autophagy receptors are represented by
524 two-sided arrows.

525

526

527

528 **Table 1. Autophagy receptors mediating selective autophagy of viral components.**

Virus	Cell, organism	Target	Ubiqu.Tag	Receptor	Outcome	Reference
SINV	neurons, mice	Capsid protein	no	p62	degradation	[10]
SINV	HeLa, MEFs, mice	Capsid protein	?	SMURF1	degradation	[21]
ICP34.5°HSV-1	HeLa, MEFs	?	?	SMURF1	degradation	[21]
SINV, ICP34.5°HSV-1, AdV	HeLa, 293T, MEFs	Capsid	?	p62	degradation	[31]
SINV, HSV-1	HeLa, MEFs, mice	Capsid	?	FANCC	degradation	[32]
CHIKV	HeLa, MEFs	Capsid Nsp2	yes ?	p62 NDP52	degradation retention	[33]
FMDV	CHO, MEFs	Capsid prot. VP1	?	p62?	degradation	[34]
MeV	HeLa	MeV-N ? MeV-C, -V ? MeV-N ?	? ? ?	p62 NDP52 TAX1BP1	anti-replication pro-replication pro-replication	[35] [39]
HIV-1	HeLa HeLa, COS7, 293T. 293T, CD4 T cells	Capsid prot. P24 APOBEC3G-Vif Tat	no no no	TRIM5 α HDAC6 p62	degradation Vif degradation degradation	[40] [41] [42] [43]
DENV, Zika virus	U2OS, 293T, HeLa, endothelial cells	NS3	?	FAM134B	anti-replication	[53]
Zika virus	Drosophila	?	?	Ref(2)P	anti-replication	[47]
CaMV	Arabidopsis	Capsid prot. P4	no	NBR1	degradation	[48]
CVB3	HeLa	Capsid. prot. VP1	yes	p62 NDP52	degradation degradation	[50]
Mutant AdV (Δ PVI prot.)	MEFs, 293T	Capsid	?, Gal-8 tag	TAX1BP1?	degradation	[12]
Coxsackievirus B1 and Poliovirus in PLA2G16° cells	293T, H1-HeLa, HAP1, A549	viral RNA	?, Gal-8 tag	?	degradation	[62]

529

530

531 **Table 2. Modulation of IFN-I inducing pathways by selective autophagy.**

At steady state						
Targeted factor	Cell	Virus	Ubiq.Tag	Receptor	Outcome	Reference
cGAS	huPBMCs, MEFs, mice	no	yes	p62	basal cGAS	[81]
HFE-bound MAVS	A549, 293T, MEFs, MDCK	no	?	p62	basal MAVS	[83]
IRF3	293T, HeLa, A549, RAW264.7, MEFs	no	yes	NDP52	basal IRF3	[84]
During viral infection						
Targeted factor	Cell	Virus	Ubiq.Tag	Receptor	Outcome	Reference
cGAS (less Ubiq.)	huPBMCs, MEFs, mice	HSV-1	yes	p62	more cGAS	[81]
MAVS (less HFE)	A549, 293T, MEFs, MDCK	SeV, VSV	?	p62	more MAVS	[83]
IRF3 (more Ubiq.)	293T, HeLa, A549, RAW264.7, MEFs	SeV	yes	NDP52	less IRF3	[84]
IRF3 (activated)	HeLa, 293T	HIV-1	?	TRIM21	less IRF3	[86]
IFITM3-bound IRF3	293T	SeV	?	?	less IRF3	[85]
MAVS	293T, HeLa, THP1, A549, RAW264.7	SeV, VSV	?	NDP52	less MAVS	[73]
MAVS	HeLa	CVB3	?	NDP52	less MAVS	[50]
RIG-I	A549, 293T	SeV, VSV, EMCV	yes	CCDC50	less RIG-I	[78]
LRRC25-bound RIG-I	293T, COS7	SeV, VSV	?	p62	less RIG-I	[76]
TRIM32-bound TRIF	293T, lung fibroblasts, BMDMs, BMDCs	dsRNA viruses	?	TAX1BP1	less TRIF	[79]

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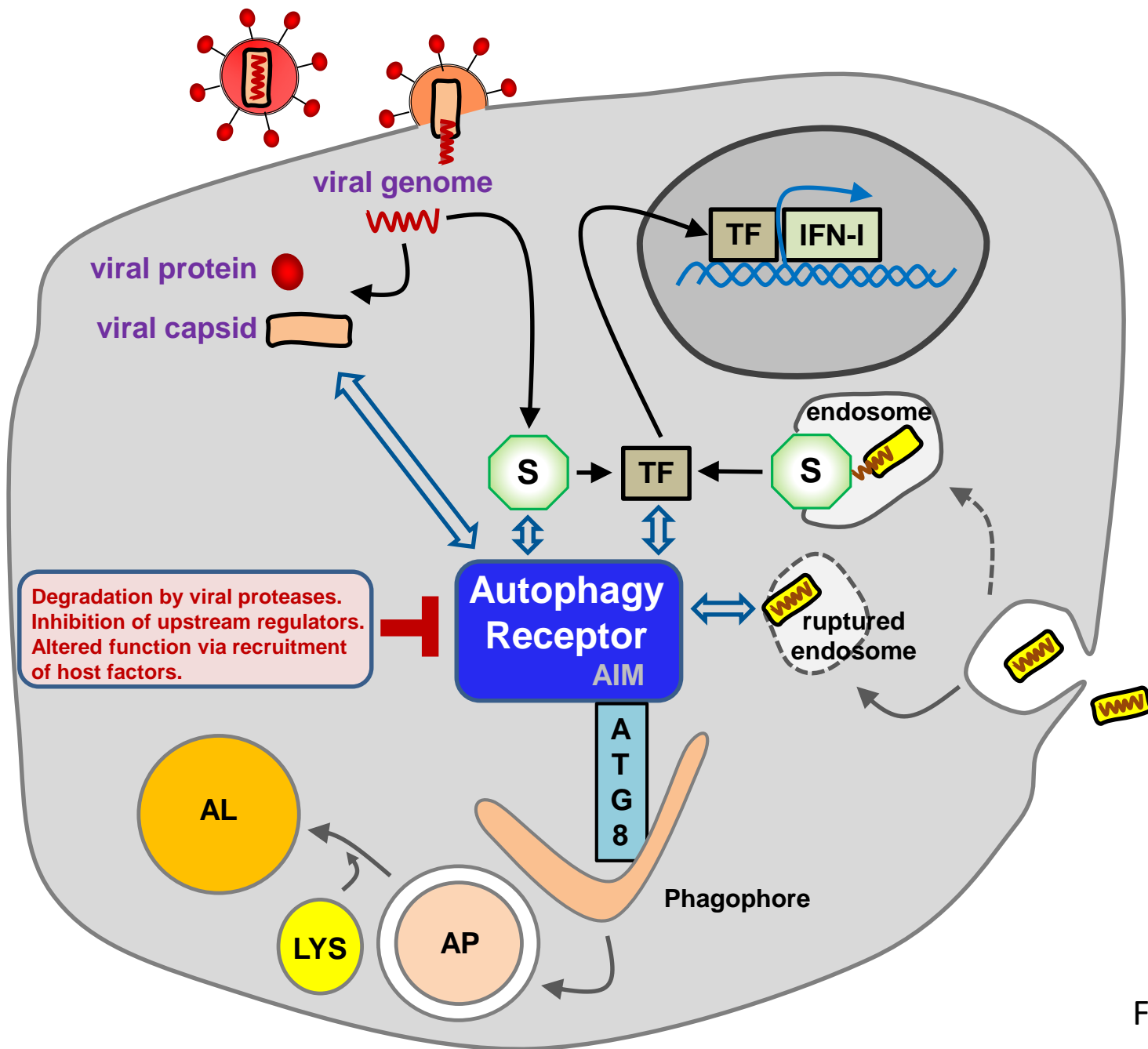


Figure 1, Key Figure.