Microreview

Nutrient sensing and metabolic stress pathways in innate immunity

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Summary

Cells monitor nutrient availability through several highly conserved pathways that include the mTOR signalling axis regulated by AKT/PI3K, HIF and AMPK, as well as the GCN2/eIF2α integrated stress response pathway that provides cellular adaptation to amino acid starvation. Recent evidence has identified a critical interplay between these nutrient sensing pathways and innate immunity to bacterial pathogens, viruses and parasites. These observations suggest that, in addition to the well-characterized pro-inflammatory signalling mediated by pattern recognition molecules, a metabolic stress programme contributes to shape the global response to pathogens.

Innate immunity is an evolutionary ancient system of host defence against infection that is present in all multi-cellular organisms (Akira et al., 2006; Medzhitov, 2007). In most animals, innate immunity is characterized by the presence of professional phagocytes, as originally revealed by Ilya Metchnikoff – a pioneer within this field of research (Gordon, 2008). However, it is important to note that some animals such as the Nematode Caenorhabditis elegans, are devoid of patrolling phagocytic cells (Engelmann and Pujol, 2010), thus highlighting the fact that innate immunity likely took various forms and used distinct strategies in animal evolution to confer efficient resistance against infection.

Another critical feature of innate immunity is the existence of defined sets of sensors that mediate detection of infectious agents to promote host defence. Recent research in Drosophila and mammalian innate immunity has identified several families of such sensors that evolved to detect conserved microbial-associated molecular patterns (MAMPs), such as Toll and peptidoglycan-recognition proteins (PGRPs) in Drosophila, and Toll-like receptors (TLRs), Nod-like receptors (NLRs), AIM2-like receptors (ALRs) and Rig-I-like receptors (RLRs) in mammals (Akira and Takeda, 2004; Akira et al., 2006; Fritz et al., 2006; Takeuchi and Akira, 2010). The discovery of these host sensors – collectively named pattern recognition molecules (PRMs), offered the spectacular validation of an ancient concept in innate immunity that common microbial signatures, such as lipopolysaccharide (LPS) found on the outer membrane of all Gram-negative bacteria, peptidoglycan (PGN), bacterial flagellin or microbial nucleic acids, could recapitulate much of the immune responses to infectious agents (Akira et al., 2006; Medzhitov, 2007). For instance, TLR4 was identified as the host sensor of LPS in mammals, while Nod1/Nod2 and PGRPs were found to detect PGN in mammals and Drosophila respectively. It is nonetheless important to highlight that this relation between PRMs and MAMPs again likely took various forms in animal evolution. Indeed, C. elegans does not have in its genome clearly identified PRMs (Engelmann and Pujol, 2010), whereas certain animal species such as the sea urchin show an exceptional expansion and diversification of several classes of genes that have clear homology with TLRs and NLRs (Rast et al., 2006). The expansion of PRMs in the genome of the sea urchin is reminiscent of the situation in plants where effector-triggered immunity appears to have favoured the selection of myriads of intracellular resistance (R) proteins that have similarity with mammalian NLRs (Anderson et al., 2010). Therefore, the detection of conserved MAMPs by a limited set of PRMs is likely not the only means by which animal hosts defend themselves against infection through innate immunity.

Amending the ‘PRM-centric’ vision of innate immunity

In addition to MAMPs, it has become progressively clear that the innate immune system also responds to danger...
signals known as danger-associated molecular patterns or DAMPs. This model, initially proposed by Polly Matzinger as an alternative to the dominant concept that innate immunity was driven by MAMPs (Matzinger, 1994), provided an explanation for how non-microbial molecules such as aluminium hydroxide (alum) could serve as adjuvants for the priming of adaptive immune responses, and how apparently aseptic tissue injury could result in so-called ‘sterile inflammation’ that shared remarkably similar hallmarks of inflammation with microbial infection. It is now accepted that both MAMPs and DAMPs contribute to the induction of innate immunity – a concept that was strikingly illustrated by the discovery that different NLRs can detect either MAMPs (such as PGN for Nod1/2 or bacterial flagellin for NLRC4) or DAMPs (such as extracellular ATP, potassium efflux or molecular crystals for NLRP3) (Benko et al., 2008).

While the notion of MAMPs and DAMPs implicitly entails the existence of corresponding PRMs, a broader concept suggests that cellular perturbations or stresses occurring in the course of an infection could help control

the host innate immune responses and allow for adaptation to these insults (Fig. 1). This notion that infection can result in important cellular stress responses has been proposed for many years with respect to studies on bacterial toxins, and in particular pore forming toxins but is only starting to emerge as a paradigm for innate immune responses to pathogens in general (Aroian and van der Goot, 2007; Bischofberger et al., 2012).

In this less ‘PRM-centric’ view, cellular innate immunity should thus be considered as the cumulative response to not only microbial conserved molecular patterns and specific cellular damages for which host receptors have been evolved, but to general cellular stresses as well. Moreover, it is clear that MAMPs and DAMPs can also trigger general cellular stress pathways. Indeed, Protein kinase R (PKR) had been identified as the first PRM for viral double-stranded RNA responsible for shutting off host cell translation – a pathway that was elucidated long before the identification of TLRs and RLRs that trigger host defence against viruses (Roberts et al., 1976; Meurs et al., 1990; Balachandran and Barber, 2007).
Although it is often overlooked and understudied in the case of bacterial pathogens, likely because it was considered as a non-specific response, the host general stress pathways triggered by pathogens are starting to gain a renewed interest. An illustration to this point is the recent discovery that inhibition of core cellular processes in C. elegans triggers cellular responses that resemble host innate immunity against bacterial pathogens (Lemaitre and Girardin, 2013). In particular, it has been proposed that translation inhibition could represent a critical alarm signal that promotes the induction of specific host defence programmes in response to bacterial pathogens (Fig. 1). However, it remains to be seen whether such a defence programme is elicited in response to all bacterial pathogens or only those that express toxins that directly inhibit the host translation machinery. Recent evidence from both in vitro and in vivo models also demonstrates that autophagy, best known as a mechanism for surviving starvation, is now considered as a critical arm of the host defence against intracellular bacterial pathogens (Dubuisson and Swanson, 2006; Deretic, 2011). The fact that bacterial autophagy – known as xenophagy, is triggered in response to membrane damage and the consequent induction of amino acid starvation pathways represents another link between innate immunity and metabolic pathways (Fig. 1) (Tattoli et al., 2012a,b).

We review here the emerging evidence that, among the cellular general stresses that arise during infection, those related with the highly conserved nutrient sensing and metabolic stress pathways are tightly associated with innate immunity.

**Host signalling pathways involved in nutrient sensing**

Monitoring the environment’s supply in nutrients is obviously a critical requirement to support survival and growth for all living organisms. It is interesting to observe that the major signalling pathways involved in nutrient sensing and metabolic stress responses are common to all eukaryotes, thus implying that those processes have been selected early in evolution and remain under a considerable selective pressure. Two critical sensing systems will be discussed in this review article: the TOR- and eIF2α-dependent signal transduction cascades, because of their well-established importance in nutrient sensing and their role in modulating innate immunity (Wek et al., 2006; Laplante and Sabatini, 2012). The connection with autophagy will also be highlighted because of the critical importance of this cellular process in both metabolic stress pathways and innate immunity.

The TOR and eIF2α signal transduction pathways monitor nutrient levels independently, although numerous levels of interaction exist, which cannot be discussed extensively here. It is worth noting however, that amino acid (AA) starvation critically regulates both TOR and eIF2α and that hypoxia and oxidative stress also impact on these two sensing systems (Wek et al., 2006; Laplante and Sabatini, 2012). The TOR pathway appears to be a highly pleiotropic nutrient sensor, as this kinase integrates multiple signals such as those dependent on the cellular levels of growth factors, cytosolic AA, energy (as per the ATP/AMP ratio) and oxygen tension.

Because the TOR- and eIF2α-dependent signalling pathways monitor nutrient availability and control metabolic stress responses, it is not surprising that these signalling cascades in turn regulate numerous cellular processes that require energy and nutrients. Those include cell proliferation, growth and division, gene expression regulation, ribosomal biogenesis, and most metabolic pathways (such as glycolysis, mitochondrial function or fatty acid metabolism) (Wek et al., 2006; Laplante and Sabatini, 2012). These sensing pathways also control cell survival and death in response to nutrient availability and, in line with this, are associated with a number of tumour suppressors (such as TSC1/2, PTEN or LKB1) and oncogenes (such as PI3K, AKT, Ras). Finally, nutrient sensing pathways and in particular TOR-dependent signalling, are strongly involved in the regulation of autophagy. As mentioned previously, autophagy is an essential process that leads to the recycling of defective cellular components and is upregulated during times of amino acid starvation. It is worth noting that there has also been evidence linking the eIF2α-dependent pathways in the control of autophagy. Talloczy et al. demonstrated that both GCN2 and PKR are required for the induction of autophagy during herpes simplex virus infection (Talloczy et al., 2002). Furthermore, the authors demonstrate through analysis of the ability of Serine-51 mutated mouse embryonic fibroblasts to induce autophagic responses that the Ser 51 phosphorylation site on eIF2α is required for both amino acid starvation and virus-induced autophagy.

**The TOR signalling cascade in innate immunity**

The TOR pathway is constituted of several branches that include LKB1/AMPK, PI3K/AKT, HIF1 and Rag GTPases, monitoring ATP/AMP levels, growth factors, oxygen tension and AA levels respectively (Laplante and Sabatini, 2012). Most of the initial studies on the link between TOR signalling and host defence focused on the impact of this pathway on viral infection. Because TOR signalling is critical for host gene translation through its effects on the TOR targets 4E-BPs and S6K, it is not surprising that many viruses have evolved strategies to maintain or promote TOR signalling. Indeed, human papillomavirus virus 16 was shown to induce mammalian TOR (mTOR)
through upregulation of growth factor receptor signalling (Surviladze et al., 2013), while vaccinia virus upregulates PI3K (Soares et al., 2009). Furthermore, hepatitis C virus was found to similarly induce the mTOR/S6K axis by inhibiting the TSC1/TSC2 complex (Bose et al., 2012), which negatively regulates mTOR signalling upstream of the protein Rheb. In human cytomegalovirus (HCMV)-infected cells, mTOR signalling was also maintained, although this virus induces several host metabolic stresses, such as endoplasmic reticulum (ER) stress, hypoxia and AA starvation (Clippinger et al., 2011), suggesting that mTOR signalling persistence in HCMV-infected cells is likely the result of an active manipulation. More surprisingly, mTOR signalling was found to be inhibited by certain viruses, such as the vesicular stomatitis virus, which downregulates AKT phosphorylation (Dunn and Connor, 2011). This might reflect the fact that viruses have selected different strategies to hijack cellular activities for their benefit, and in particular, the inhibition of TOR signalling can confer an advantage to viruses that require autophagy induction for their propagation (see below). Moreover, it must be noted that mTOR signalling has been shown to amplify antiviral type I interferon responses, suggesting that upregulating mTOR pathways to sustain host translation machinery might be a double-edge sword strategy for viruses.

Recent reports have started to uncover a role for the energy sensor AMPK in antiviral responses. As mentioned above, HCMV induces host metabolic stress responses (Clippinger et al., 2011) and it was shown that the activation of AMPK in this context is critical for viral replication (McArdle et al., 2012). Similarly, it was proposed that AMPK activation is important to facilitate entry of vaccinia virus and the Ebola virus, through its effects on macro-pinocytosis (Kondratowicz et al., 2013). In contrast, AMPK could efficiently restrict infection by the Rift Valley Fever Virus (RVFV) and other viruses by inhibiting fatty acid metabolism, which appears to be important at several stages during the course of RVFV infection (Moser et al., 2012). Finally, hepatitis C virus was found to inhibit AMPK activity by promoting its dephosphorylation, which is required for HCV replication (Mankouri et al., 2010).

Changes in oxygen tension observed in hypoxia are also known to affect viral replication. Hypoxic conditions usually restrict the replication of viruses that have a tropism for tissues exposed to atmospheric oxygen (such as adenovirus or simian virus 40), while hypoxia favours the propagation of viruses that target tissues exposed to low oxygen levels (human immunodeficiency virus, herpesviruses, parvovirus B19 or vesicular stomatitis virus) (Zinkernagel et al., 2007). In addition, viral infection commonly results in stabilization of hypoxia inducible factor (HIF) and induction of cellular hypoxic responses even in normoxic conditions, which has been shown to restrict or promote viral growth, depending on the virus and targeted host cells (Zinkernagel et al., 2007).

Recent studies have shed light onto the role of TOR signalling in the host response to bacterial pathogens and toxins. In human epithelial cells infected with *Shigella* or *Salmonella*, two enteric pathogens that invade host cells, mTOR activity is rapidly blunted as a consequence of the activation of an AA starvation response that is caused by host membrane damage (Tattoli et al., 2012b). In the case of *Salmonella*, this stress response is only transient and associated with the damage to the *Salmonella*-containing vacuole (SCV), likely inflicted by the insertion of the bacterial type three secretion system (Tattoli et al., 2012a). It was further demonstrated that the inhibition of mTOR signalling in the infected cells promotes a pro-autophagic cellular environment important to clear the infection (see also section below on autophagy). Infection of *Drosophila* with the lethal pathogen *Pseudomonas entomophila* similarly results in the induction of metabolic stress responses, characterized by the inhibition of TOR signalling and the induction of GCN2 and AMPK pathways (Chakrabarti et al., 2012). The metabolic stress responses, driven by reactive oxygen species and the activity of a bacterial pore-forming toxin, causes general translation arrest in infected animals, which is likely responsible for the deleterious effect of this bacterial pathogen on its host. Finally, consistent with the notion that membrane damage induces metabolic stress responses through AA starvation, bacterial pore-forming toxins have been shown to inhibit mTOR signalling and to trigger the GCN2/eIF2α-dependent integrated stress response characteristic of AA starvation (Kloft et al., 2010).

Little is known about the impact of hypoxia or HIF on the host response to bacterial pathogens. In keratinocytes, HIF-1α has been shown to protect against necrotic skin lesions induced by group A *Streptococcus*, through the regulation of antimicrobial peptide production in the skin (Peyssonnaux et al., 2008). Interestingly, hypoxia was also shown to enhance phagocytosis in macrophages in a HIF-1α-dependent manner, thus highlighting a potentially general effect of hypoxia on innate immunity (Anand et al., 2007).

Infection with protozoan parasites also impacts on mTOR signalling. *Toxoplasma gondii* is able to maintain mTOR-dependent cellular growth and phosphorylation of the ribosomal S6 protein in infected cells, although not through the canonical induction of the prototypical mTOR targets, S6K1 and 4E-BP1, suggesting the existence of parasite-specific mechanisms of mTOR regulation (Wang et al., 2009). In contrast, *Leishmania* protease GP63 was shown to cleave and thus inhibit mTOR in infected macrophages (Jaramillo et al., 2011). The resulting derepression of the activity of 4E-BP1, a potent inhibitor of
gene translation, contributes to the increase in parasite replication.

The caspase-1 inflammasome is a molecular platform responsible for the maturation and secretion of the cytokines IL-1β and IL-18. A recent study demonstrated that murine NLR protein, Nlrp1b, triggers the inflammasome in response to energy stress caused by metabolic inhibitors or by nutrient deprivation (Liao and Mogridge, 2013). Importantly, lowering the levels of cytosolic ATP is sufficient to activate Nlrp1b-dependent formation of the inflammasome. These metabolic conditions also trigger the energy stress sensor AMPK, which was shown to facilitate Nlrp1b activation. Because NLRP3, a close homologue of Nlrp1b, is indirectly activated by extracellular ATP, these results suggest that NLR proteins might play a role in linking cellular metabolism and inflammatory pathways. How these NLR proteins cross-talk with the mTOR signalling network remains to be further explored.

**eIF2α-dependent pathways in innate immunity**

The integrated stress response (ISR), which functions to regulate translation via eIF2α, is another well-characterized pathway that incorporates both nutrient sensing and innate immunity. Translation initiation involves the interaction of eIF2 with the initiator Met-tRNA and GTP to form a ternary complex (Wek et al., 2006; Nallagatla et al., 2011). Upon proper pairing of Met-tRNA with its AUG start codon, the eIF2–GTP complex is hydrolysed and recycled through interaction with the guanine nucleotide exchange factor eIF2B for subsequent rounds of translation initiation. Various stress stimuli can induce phosphorylation of the eIF2α subunit, causing the transcription factor to act as an inhibitor of eIF2B and preventing the recycling of eIF2–GTP. This reduction in eIF2–GTP consequently leads to inhibition of translation initiation on a global scale. Four protein kinases are known to induce eIF2α phosphorylation in response to different environmental stresses: GCN2, haem-regulated inhibitor (HRI), protein kinase R (PKR) and PKR-like endoplasmic reticulum kinase (PERK) (Balachandran and Barber, 2007). GCN2 and PERK are triggered by amino acid depletion and ER stress within the cell, respectively, while HRI responds to oxidative stress. As already mentioned above, it is interesting to note that the double-stranded RNA sensor PKR, which plays an integral role in innate immunity against viruses, is found among these kinases. The convergence of various metabolic stressors including AA starvation, endoplasmic reticulum stress and PKR-mediated immune pathways at the level of translation highlights an interesting link between metabolic stress and innate immunity.

It has been well established that pathways involving PKR are crucial to antiviral host innate immunity. Upon interaction with dsRNA in the cytoplasm, PKR is activated and can induce a number of downstream signalling cascades (Pindel and Sadler, 2011). Because viral pathogenesis often requires hijacking of host translational machinery, the translational blockade induced via PKR-mediated phosphorylation of eIF2α is essential for limiting viral replication and spread. It is therefore not surprising that viruses have evolved a number of strategies to evade host immune responses. One common mechanism employed by viruses to avoid detection is to inhibit PKR directly. Examples of this include the Kaposi’s sarcoma virus protein viRF-2 and the hepatitis C virus E2 protein, which both bind directly to PKR and prevent its activation through inhibition of autophosphorylation (Gale et al., 1996; Burysek and Pitha, 2001). Furthermore, several viral proteins function to inhibit the functional activation of PKR via eIF2α phosphorylation, including the herpes simplex virus protein ICP34.5 that recruits the phosphatase PP1 to dephosphorylate eIF2α, thus preventing the activation of PKR (Li et al., 2011). Lastly, a number of viruses can evade detection via synthesis of dsRNA-binding proteins. Both the influenza protein NS1 and the vaccinia virus protein E3L function to sequester away dsRNA through direct interaction and effectively block PKR activation (Lu et al., 1995; Shors et al., 1997).

In the case of bacterial pathogens, infections have been shown to trigger the ISR amino acid starvation and ER stress pathways, converging on eIF2α phosphorylation by the respective GCN2 and PERK kinases, independent of PRM activation (Chakrabarti et al., 2012; Shrestha et al., 2012; Tattoli et al., 2012b). The intracellular bacterial pathogens *Shigella* and *Salmonella* were shown to trigger an amino acid starvation programme in infected cells, resulting in induction of the GCN2/eIF2α ISR axis (Tattoli et al., 2012b). Transcriptomic analysis of *Shigella*-infected epithelial cells revealed that, in addition to a strong inflammatory programme, infected cells display a transcriptional signature of ISR, highlighted by the induction of stress response genes such as ATF3, CHAC1, CHOP, GADD45A and GADD45B. Moreover, RNA stress granules are observed in *Shigella*-infected cells (Tattoli et al., 2012b), and these granules are known to accumulate in an eIF2α-dependent manner as a result of translation initiation inhibition in metabolically stressed cells.

In addition to the ISR, the unfolded protein response (UPR) is a critical pathway that results from the accumulation of unfolded proteins in the endoplasmic reticulum. Induction of the UPR triggers translational arrest through several pathways including the PERK/eIF2α signalling cascade. Recently, it was shown that the intracellular bacterial pathogen *Listeria monocytogenes* triggered UPR in infected cells via its pore-forming toxin Listeriolysin O.
Autophagy at the nexus of metabolism and innate immunity

Autophagy is a highly conserved process of all eukaryotic cells, which is tightly regulated by metabolism and is turned on during starvation. This process promotes the degradation and recycling of cellular components, including macromolecular complexes and damaged organelles, in order to maintain the pools of essential nutrients, such as AA or glycolysis intermediates, during starvation (Yang and Klionsky, 2010). Importantly, autophagy has recently emerged as a critical arm of the host response to intracellular bacterial pathogens, thus demonstrating the importance of metabolic stress pathways in the control of bacterial infection (Deretic, 2011).

A number of invasive bacterial pathogens induce xenophagy, a specific type of autophagy in which microorganisms are targeted by the proteins of the autophagic machinery once in the cytosol or in intracellular vacuolar compartments (Deretic, 2011). Interestingly, bacteria that escape the entry vacuole and are found free in the host cytosol, such as Shigella, Listeria, Staphylococcus aureus and group A Streptococcus or bacteria that remain confined into modified vacuoles, such as Salmonella, can all be targeted by xenophagy, although the detection mechanisms likely vary. Xenophagy is an efficient host defence mechanism because it allows isolating bacteria into a double membrane vesicle that is destined to fuse with lysosomes, resulting in the killing of the invading pathogen. This innate immune role of xenophagy is highlighted by the observation that cells displaying defective xenophagy cannot control bacterial growth in cellular models of infection (Deretic, 2011).

Bacterial autophagy represents a striking example of the interconnection between host innate immune defence and metabolism. Indeed, as mentioned above, autophagy is a critical scavenger and recycling process required to maintain metabolic homeostasis, in particular during nutrient starvation. A critical question that arises from xenophagy studies is to understand how this innate defence system could remain efficient, irrespective of the metabolic status of the cells. Indeed, autophagy is strongly inhibited in metabolically replete cells, and in particular by the mTOR pathway, and it is difficult to envision that such critical defence mechanism would only be operational in cells undergoing nutrient starvation. One of the first evidence towards the elucidation of this apparent conundrum came with the demonstration that host membrane damage, which occurs when bacteria escape to the cytosol or insert a secretion system through host membranes, triggers a state of AA starvation that results in inhibition of mTOR signalling, thus promoting a pro-autophagic environment (Tattoli et al., 2012a,b). Interestingly, membrane damage triggered by bacteria or their toxins appears to represent a
critical regulation level for xenophagy (Portnoy et al., 2002; Birmingham et al., 2006; von Hoven et al., 2012; Tattoli et al., 2012b). In addition to provoking mTOR inhibition through AA starvation, membrane damage serves as a cellular signal favouring the recruitment of adaptor proteins that allow for the targeting of bacteria to the autophagic machinery— including ubiquitinated proteins, p62 or NDP52 (Boyle and Randow, 2013).

Autophagy can either restrict or promote viral replication during infection. In certain viral infections, autophagy plays an essential role in host defence by directly targeting viruses or their components to autophagosomes for degradation. Similar to the mechanism described above for bacteria, Sequestosome 1/p62-like Receptors, or SLRs, act as a type of PRM to recognize viral components and target them for autophagic destruction. An example of such SLR-mediated viral targeting was recently shown for Sindbis virus where p62-mediated recognition of the viral capsid marked it for degradation in a ubiquitin-independent fashion (Orvedahl et al., 2010). Interestingly, a recent siRNA screen identified SMURF1 as a common mediator of autophagy for viruses including herpes simplex virus 1 (HSV1) and Sindbis as well as for mitochondrial autophagy (Orvedahl et al., 2011). Another mode by which autophagy can restrict viral infection is through the selective targeting of viral nucleic acid to endosomes, where their interaction with TLRs drives an antiviral interferon response. Indeed, vesicular stomatitis virus (VSV) infected plasmacytoid DCs were shown to require autophagy to deliver viral replication intermediates to TLR7 in late endosomes, resulting in type I interferon production (Lee et al., 2007). Finally, autophagy can also be considered as an antiviral mechanism in that autophagic destruction of viral components provides antigens for MHC class I and class II presentation and induction of an adaptive immune response to help clear the infection (reviewed in Gannage and Munz, 2010).

Interestingly, certain components of the autophagy machinery can also function in viral infection but in a manner that is independent of canonical autophagy. Indeed, using a murine norovirus (MNV) infection model, portions of the autophagy machinery, specifically, Atg5–Atg12/Atg16L1, where shown to be required by interferon-γamma in order for this cytokine to block MNV infection (Hwang et al., 2012). In contrast, a non-canonical role of the ATG12–ATG5 conjugate in suppressing antiviral immune signalling has also been shown. Specifically, the ATG12–ATG5 conjugate negatively regulates the type I interferon pathway through its interference with RIG-I/MAVS-mediated sensing of VSV RNA (Jounai et al., 2007).

Viruses have also evolved sophisticated systems to evade autophagy as well as using the autophagy machinery to propagate within the host. Indeed, certain viruses use autophagy-escape strategies that include avoidance of autophagy capture, inhibition of autophagy initiation and suppression of autophagosome maturation (reviewed in Dong and Levine, 2013). As a way to promote viral propagation, autophagy in general can maintain nutrient supply and inhibit cell death, thereby providing viruses with building blocks for replication. More specifically, certain viruses use autophagy components to promote their replication. For hepatitis C virus, its RNA polymerase, NS5B, interacts transiently with ATG5 and appears to promote viral replication (Guevin et al., 2010). More generally and while the precise mechanisms are largely unknown, in different viral infection models including Hepatitis B, Cosackie B3 and Kaposi sarcoma-associated herpes, knocking-down or -out autophagy components can reduce viral replication (reviewed in Dong and Levine, 2013).

Concluding remarks

As described in this Review, nutrient sensing and metabolic stress pathways emerge as crucial regulators of innate immunity. While there is strong evidence to support involvement of both the mTOR and GCN2 pathways during infection, it remains to determined what role the pathogens play in the direct activation of these pathways and whether bacteria have evolved mechanisms to overcome such responses. Additional studies will help to shed light on the means by which pathogenic infection activates the aforementioned stress responses and may reveal novel insights into the interplay between stress pathways and innate immunity. Furthermore, although we focused here on pathways dependent on mTOR signalling, eIF2α-dependent stress pathways and autophagy, it is important to highlight the fact that nutrient sensing and innate host defence interconnect at multiple other levels that could not be covered in this article. For instance, the crucial antiviral adaptor molecule MAVS needs to be anchored at the mitochondria to transduce antiviral responses (Seth et al., 2005), and it is possible that this subcellular localization is important to connect antiviral responses with mitochondrial metabolic activity. Also of interest was the recent demonstration that inhibition of the insulin-like response pathway in Drosophila and the subsequent activation of FOXO, was important to maintain homeostatic expression of antimicrobial peptides in the insect gut (Becker et al., 2010), and a potential role for FOXO-dependent signalling in mammalian innate immunity is now starting to emerge (Seiler et al., 2013). Finally, it is important to highlight that, in addition to its role in innate immunity, nutrient sensing plays fundamental roles in adaptive immunity by regulating T cell function, likely owing to the fact that these cells undergo massive changes in their metabolism upon activation and during clonal expansion (Yang and Chi, 2012). Future studies will undoubtedly reveal new aspects of this fundamental link between immune responses, nutrient sensing and metabolic stress.
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