Cell. Mol. Life Sci.
DOI 10.1007/s00018-015-2119-4
Cellular and Molecular Life Sciences

REVIEW

Exploring NAD^+ metabolism in host–pathogen interactions

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Received: 9 July 2015 / Revised: 27 November 2015 / Accepted: 14 December 2015

Abstract Nicotinamide adenine dinucleotide (NAD^+) is a vital molecule found in all living cells. NAD^+ intracellular levels are dictated by its synthesis, using the de novo and/or salvage pathway, and through its catabolic use as co-enzyme or co-substrate. The regulation of NAD^+ metabolism has proven to be an adequate drug target for several diseases, including cancer, neurodegenerative or inflammatory diseases. Increasing interest has been given to NAD^+ metabolism during innate and adaptive immune responses suggesting that its modulation could also be relevant during host–pathogen interactions. While the maintenance of NAD^+ homeostatic levels assures an adequate environment for host cell survival and proliferation, fluctuations in NAD^+ or biosynthetic precursors bioavailability have been described during host–pathogen interactions, which will interfere with pathogen persistence or clearance. Here, we review the double-edged sword of NAD^+ metabolism during host–pathogen interactions emphasizing its potential for treatment of infectious diseases.

Keywords Nicotinamide adenine dinucleotide (NAD^+) · Host-pathogen interaction · NAD^+/NADH ratio · NADPH · Sirtuins · L-tryptophan

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Nicotinamide adenine dinucleotide (NAD^+) was initially discovered by Sir Arthur Harden as a 'cozymase' for yeast fermentation over 100 years ago. The succeeding work contributed to the identification of NAD^+ as a player in hundreds of biochemical reactions through its role in redox reactions. NAD^+ is either consumed as a co-substrate by NAD^+-consuming enzymes or used as an electron carrier in redox reactions. Yet, the intracellular NAD^+/NADH ratio is key to the maintenance of an adequate metabolic status and cell survival. Growing evidences indicate that NAD^+ biosynthetic pathways and metabolism are playing a major role in host–pathogen interactions. In this review, we overview these mechanisms highlighting the role of NAD^+ metabolism as an attractive therapeutic target for microbe infections.

NAD^+ biosynthesis: where the tale begins

NAD^+ biosynthesis in mammalian cells

The biosynthesis of NAD^+ in mammals occurs through two different pathways: the de novo and the salvage pathways (Fig. 1). The de novo pathway begins with the uptake and conversion of dietary L-tryptophan in N-formylkynurenine, which is mediated by the rate-limiting indoleamine 2,3-dioxygenase (IDO) or tryptophan 2,3-

Published online: 30 December 2015

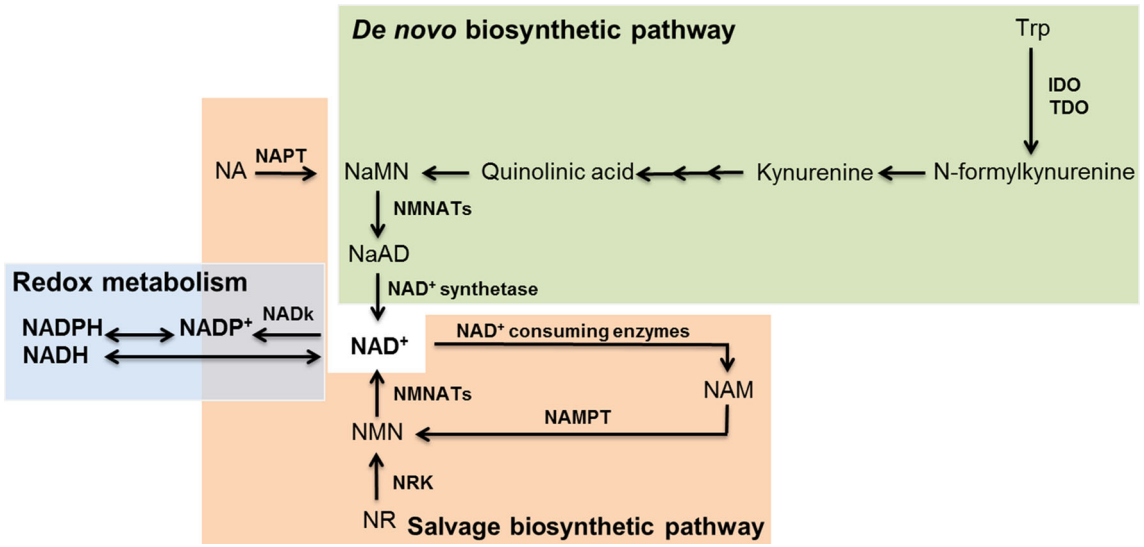

Fig. 1 NAD^+ biosynthetic pathways and redox metabolism of mammals. The de novo pathway for NAD^+ biosynthesis is indicated in *green*, the salvage pathway is indicated in *orange* and the redox metabolism of NAD/NADP is indicated in *blue*. *IDO* indoleamine 2,3-dioxygenase, *NAD*$^+$ nicotinamide adenine dinucleotide, *NaAD* nicotinic acid dinucleotide, *NADP* nicotinamide adenine dinucleotide phosphate, *NADK* NAD^+ kinase, *NAM* nicotinamide; *NaMN* nicotinic acid mononucleotide, *NAMPT* nicotinamide phosphoribosyltransferase, *NAPT* nicotinic acid phosphoribosyltransferase, *NMNAT* nicotinamide mononucleotide adenylyltransferase, *NMN* nicotinamide mononucleotide, *NR* nicotinamide riboside, *NRK* nicotinamide riboside kinase, *TDO* tryptophan 2,3-dioxygenase, *Trp* tryptophan

dioxygenase (TDO). After several subsequent enzymatic reactions, quinolinic acid is formed and further condensed in nicotinic acid mononucleotide (NaMN). NaMN is converted in nicotinic acid adenine dinucleotide (NaAD) by the activity of nicotinamide mononucleotide adenylyltransferase isoforms (NMNATs 1–3). The completion of the de novo pathway occurs with the production of NAD^+ by the glutamine-dependent NAD^+ synthase [50].

NAD^+ levels can also be restored through the import or recycling of nicotinic acid (NA), nicotinamide (NAM) or nicotinamide riboside (NR) in the salvage pathway. NA is converted to NaMN by the NA phosphoribosyltransferase (NAPT) to generate NAD^+ through the Preiss–Handler pathway converging with the de novo pathway. NAM is used as a source of NAD^+ through the activity of NAM phosphoribosyltransferase (NAMPT), which is the rate-limiting enzyme of the salvage pathway [77]. In addition, nicotinamide ribose kinase (NRK) induces the phosphorylation of NR in NAM mononucleotide (NMN), which is the converging point of the salvage pathway culminating in the production of NAD^+ through the adenylation of NMN by NMNAT. Finally, NAD^+ is further phosphorylated to $NADP^+$ by the cytosolic NAD kinase (NADk) to enter redox metabolism.

NAD^+ pools: a dynamic regulation for achieving ideal distribution

Metabolic functions and the modulation of several biological processes are dependent on the cellular homeostasis of NAD^+/NADH ratio. Eukaryotic cells maintain an independent mitochondrial and cytosolic NAD^+ pool, which allows coping with distinct stimuli and challenges [103]. NAD^+ pools are used for protein post-translational modifications, such as protein mono- or poly(ADP ribosyl)ation or deacetylation, or for the production of second messengers, such as the Ca^{2+}-mobilizing compounds cyclic adenosine diphosphoribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP). Nonetheless, the contribution of NAD^+ fluxes between compartments and its consequent homeostasis is yet to be completely understood.

As different processes require different intermediates and, therefore different NAD^+ levels, it has become clearer that this molecule is stored in a compartment-specific fashion. Cytosol and mitochondria represent the main intracellular NAD^+ pools [19]. The NAD^+/NADH ratio is about 100-fold lower in mitochondria when compared with the cytosolic compartment. Indeed, it has been estimated that the cytosolic compartment display NAD^+/NADH ratios ranging between 60 and 700 whilst mitochondrial are set at 7 to 8 [100]. This ratio reflects the overall redox state of the cell and its maintenance is crucial for cell survival through the control of energy metabolism. The defined compartmentalization allows a preservation of oxidative phosphorylation in the event of a massive cytosolic NAD^+ depletion with maintenance of cell viability and ATP stores for a short period of time. The "Mitochondrial Oasis Effect" refers to the capacity of mitochondria to dictate

cell survival through maintenance of specific NAD^+ pools, even after depletion of nuclear and cytosolic ones. This protection was shown to be dependent on NAMPT activity via mitochondrial SIRT3 and SIRT4 [103].

The compartmentalization of NAD^+ synthesis is achieved by tightly controlled localization of the three NMNAT isoforms; nuclear NMNAT1, cytosolic NMNAT2 and mitochondrial NMNAT3 [58]. The rigorous subcellular localization of mammalian NMNAT isoforms suggests a predominant role for this enzyme in determining the subcellular NAD^+ pool distribution. NMNAT1 is the most efficient enzyme involved in the forward and reverse equilibrium reaction that originates adenylyltransference or pyrophosphorylysis, respectively. Although NMNAT1 utilizes nicotinamide mononucleotide (NMN) as a major precursor for NAD^+ synthesis, it was shown that NMNAT2 displays a high affinity for nicotinic acid mononucleotide (NaMN) that originates nicotinic acid adenine dinucleotide (NAAD), whilst hNMNAT3 was demonstrated to be the isoform with lower selectivity for purine nucleotides [46]. Although it is still debated whether NMNAT1-synthesized NAD^+ may be exchanged between the nucleus and cytoplasm via nuclear pores, it is known that NAD^+ synthesis is independently regulated in these compartments and the cytoplasmic NAD^+ pool is maintained primarily by NMNAT2. In mammals, mitochondrial NAD^+ is not exchangeable with the cytosol and thus NMNAT3 presumably participates in the maintenance of the organelle nucleotide pool [18, 45]. Indeed, it has been reported that FK866, a well-known inhibitor of rate-limiting NAMPT, does not affect mitochondrial NAD^+ pool, possibly indicating that this enzyme is not a major regulator of NAD^+ in this organelle [70].

NAD^+ metabolism in pathogens: evolution towards auxotrophy

NAD^+ metabolic networks present a remarkable intrinsic complexity and evolutionary variability [91]. Notably, the biosynthesis of NAD^+ has evolved in several pathogenic organisms towards auxotrophy or to a restriction in the capacity to use a biosynthetic precursor. Several microorganisms encoded enzymes ae capable to utilize NAD^+ from infected hosts. *Candida glabrata*, a fungus that lacks the genes for de novo synthesis, is a NAD^+ auxotroph possessing a functioning salvage pathway that requires the uptake of external sources of NAD^+ or precursors from the host cell milieu [20]. *Haemophilus influenzae* is a gram-negative bacterium that possesses an absolute need for NAD^+ due to a lack of de novo biosynthetic enzymes or of salvaging NAM, niacin or other intermediates of the Preiss–Handler pathway. As NAD^+ cannot be taken up into the bacterium cytosolic compartment as an intact molecule, previous studies have established that NMN and NR are the biochemical sources for NAD^+ in *H. influenzae*. Two proteins were identified to play a key role in the uptake of NAD^+; the outer membrane lipoprotein e(P4) and a periplasmic NAD nucleotidase (NadN). The e(P4) outer membrane protein and the NadN periplasmic enzyme convert NAD^+ to NMN and NR [38]. The latter is able to cross the inner membrane to the cytoplasm, where NadR recycles it back to NAD^+ by phosphorylating NR to NMN that is further adenylated to NAD^+ [44, 87]. *Shigella* spp., the pathological agent of bacillary dysentery, lacks a de novo pathway for the synthesis of NAD^+ and therefore requires nicotinic acid for growth [51]. As most prokaryotes, *Shigella* converts L-aspartate into the precursor for NAD^+ synthesis quinolinic acid depending on the enzyme complex composed by quinolate synthase (NadA) and L-aspartate oxidase (NadB). Quinolinic acid is subsequently converted into nicotinic acid mononucleotide by quinolinate quinolinic acid concentration decreases the intracellular spreading of *Shigella*, which confirmed the occurrence of a selective pressure towards the inactivation of the *nadA* and *nadB* genes during evolution [72, 73]. Therefore, the available intracellular concentration of NA is not limiting for bacterial growth and in fact the reintroduction of functional copies of *nadA* and *nadB* into this strain restored the ability to synthesize quinolate, but resulted in strong attenuation of virulence, thus defining the *nadA* and *nadB* as an anti-virulent loci [73]. Comparative genomic studies have established that *Leishmania* protozoan parasites are also NAD^+ auxotrophic organisms. Exogenous supplementation of NA, NAM or NR precursors increase the intracellular NAD^+ content in *Leishmania* parasites [26]. In the case of *Mycobacterium tuberculosis*, NAD^+ synthesis relies on both pathways, with the common enzyme being NAD^+ synthase [99].

Several pathogens encode a nicotinamidase to convert NAM in NA for NAD^+ synthesis. *Leishmania* nicotinamidase deletion led to a reduction of 70 % in NAD^+ content, affecting both promastigote growth and the establishment of infection in mice [26]. This enzyme should further prevent the accumulation of anti-leishmanial NAM [85] by recycling it to NAD^+. In addition, *Borrelia burgdorferi* and *Brucella abortus* nicotinamidases were shown to be essential for bacteria replication and infectivity [40]. These examples support that the inhibition of nicotinamidase may drive specific microbicidal effects towards intracellular pathogens. NMNAT encoded by *Plasmodium* (PfNMNAT) is quite divergent from the human homologs but share significant homology with bacterial counterparts. The inhibition of PfNMNAT results in the arrest of parasite growth in earlier events, thus indicating an importance of this biosynthetic enzyme in the development of *Plasmodium* parasites [63]. Therefore, NAM, nicotinamidase and NMNAT activities are determinants for pathogen survival

in its mammalian host. These observations highlight that NAD^+ is essential for parasite growth being required for the activity of several key substrates.

The importance of NAD^+ in host–pathogen interactions

Modulation of host NAD^+ levels by intracellular pathogens

Fluctuations in NAD^+ levels in infected cells have been described for different classes of intracellular pathogens. Peripheral blood lymphocytes from HIV-infected individuals display a decrease of intracellular NAD^+ levels, which may be reverted by exogenous administration of NAM [62]. In contrast, *Plasmodium*-infected erythrocytes display higher NAD^+ levels than uninfected ones. This increase appears to be mediated by an increase in NAMPT and NAPT activity in infected cells, which allows the production of NAD^+ through NAM and NA salvage, respectively [107]. *Leishmania infantum* induced a transitory NADH increase immediately after infection that was posteriorly reverted to higher NAD^+/NADH ratio once the infection is established [56]. Therefore, the modulation of host NAD^+ levels may vary accordingly to the infectious agent and probably the type of host cell due to their intrinsic metabolic requirements. Group A streptococci (*Streptococcus pyogenes* or GAS) represent a remarkable case of intracellular NAD^+ modulation. GAS NAD^+ glycohydrolase has the ability to cleave NAD^+ producing nicotinamide and ADP-ribose but also cyclic ADP-ribose (cADPR) upon being injected in the cytosol of an infected host cell [95]. This results in a profound depletion of cellular NAD^+ and ATP levels, leading to growth arrest and cell death [54]. As a consequence of depletion of host cell energy stores through the enzymatic action of NADase, GAS has proven to disrupt several innate processes of immune defense. As such, NAD^+ glycohydrolase activity modifies several NAD^+-dependent host cell responses including poly (ADP-ribose) polymerase (PARP)-1 activity [13], preventing phagolysosome acidification [3] and autophagy killing [64], which contributes to treatment failure, relapse and chronic persistence. Further studies in different types of pathogens are required to fully understand if the modulation of host NAD^+ levels by intracellular pathogens is imperative for successful colonization.

Enzymes involved in NAD^+ synthesis contribute to the immune response against pathogens

Tryptophan catabolism, which ultimately results in NAD^+ production, has been shown to have a major role in the regulation of immune responses. The immunosuppressive effects of IDO have been vastly associated with impaired proliferation, induction of apoptosis and induction of regulatory T cells [71]. However, several pathogenic species are tryptophan auxotrophs, such as *Chlamydia*, *Leishmania* or *Toxoplasma gondii*. Thus, tryptophan depletion by IDO may further impact their intracellular survival [5]. IFN-γ-nduced IDO was also demonstrated to be responsible for inhibition of *Staphylococcus aureus* replication, the major causative agent of cerebral abscesses [83]. Recently, CD4 T cells were shown to contain *M. tuberculosis* growth by starving out of tryptophan [108]. Although *M. tuberculosis* can synthesize tryptophan under immune stress, blocking the bacterial tryptophan synthesis restored the efficacy of the immune system to kill the mycobacteria. Tryptophan catabolism by IDO is also a central mechanism for limiting tissue damage. The blockage of IDO was shown to attenuate *T. gondii* replication in the lung due to decreased inflammatory tissue damage [60]. Distinctively, in a *Clostridium difficile* infection model, $IDO^{-/-}$ mice showed increased immunopathology, as evidenced by increased mucosal destruction, cecal hemorrhage and higher levels of neutrophil-driven IFN-γ production. Therefore, tryptophan catabolism by IDO is a central mechanism for limiting tissue damage and for decreasing *C. difficile* bacterial burden, consequently restricting the observed pathology [22]. The absence of IDO was also correlated with a suppression of LP-BM5 murine leukemia virus replication via upregulation of type I IFNs [35]. IDO was found to be increased during HIV infection, which was associated with the dysfunction of CD8 immune T cells in controlling pathogens, the loss of Th22 cells and a consequent shift to Treg cells [4, 16]. Several other viral infections, including hepatitis B and C as well as influenza infections display an increased expression and activation of IDO, where tryptophan metabolism appears to have a crucial role in the fight against pathogens [81]. If in one hand the depletion of tryptophan may alter the phenotype of immune cells driving them towards immunosuppression, on the other hand it may have a severe impact on the growth of intracellular pathogens.

Besides IDO, other enzymes in the biosynthetic pathway of NAD^+ synthesis have been demonstrated to play a role during infection. NAMPT was shown to inhibit HIV replication at an early step through abrogation of the integration of proviral DNA [97]. However, an increase in NAMPT expression could prevent HIV-1 replication rather than inhibiting it [14]. NAMPT targeting could provide strong anti-inflammatory effects leading to a decrease of the inflammatory tissue damage, without compromising host defense as exemplified during *S. aureus* infection [78].

Overall, a special attention should be paid to the dual effect of targeting host enzymes involved in NAD^+

synthesis, especially now that novel IDO and NAMPT inhibitors are being tested for cancer chemotherapy [102], which may increase the potential immunosuppression of the patients.

The importance of NAD^+-consuming proteins in infected cells

NAD^+ is a cofactor for three classes of proteins: sirtuins, PARPs and membrane proteins CD38/CD157, where it contributes as a source of ADP-ribose. These NAD^+-consuming proteins are considered *metabolic sensors* with a vital role in energy metabolism, cell survival, proliferation and effector functions. The mechanistic action of NAD^+-consuming proteins during host–pathogen interaction is illustrated in Fig. 2.

cADP-ribose synthases

These ectoenzymes, known as lymphocyte antigens CD38 and CD157, are multifunctional proteins involved in the generation of second messengers in intracellular signaling. cADP-synthases are the major NAD^+-regulating proteins: for each cADP-ribose molecule produced, around 100 NAD^+ molecules are broken [17, 21]. Hence, CD38 is a main cellular NADase in mammalian tissues being a critical regulator of NAD^+ levels by modulating its bioavailability. Under homeostatic conditions, very little NAD^+ is found free in the serum of normal mice [42]. Previous studies have shown that NAD^+ is consistently released or actively transported to the extracellular medium and rapidly catabolized by CD38 to maintain its levels to a minimum [84]. Nevertheless, upon damage or infection, local levels of extracellular NAD^+ can rise quite dramatically, leading to an increased activity of CD38. The generated cADP-ribose and nicotinic acid adenine dinucleotide phosphate (NAADP) contribute to Ca^{2+} mobilization [47] and will enhance the ability of monocytes, neutrophils and dendritic cells to migrate to sites where danger was felt and secondary lymphoid tissues in response to chemokines [69]. Studies performed with $CD38^{-/-}$ mice demonstrated its crucial role in the regulation of both innate and adaptive immune responses against infections [69]. As illustrative examples, $CD38^{-/-}$ mice are more susceptible to infection by *S. pneumoniae* [68] and *M. avium* [98], while presenting a decrease hepatic elimination of *Entamoeba histolytica* [24] due to reduced neutrophil recruitment and limited inflammatory response. A similar failure to induce an appropriate inflammatory response was observed in *Naegleria fowleri*-induced primary amoebic meningoencephalitis [12]. Therefore, understanding how to alter NAD^+ extracellular levels or CD38 enzyme activity is an exciting prospect in the modulation of inflammatory responses during infections.

PARPs

NAD^+ is also used as a substrate for mono- or poly(ADP-ribosyl)ation (PARylation) reactions mediated by ADP-ribose transferases (ARTs) or poly(ADP-ribose) polymerases, respectively. ARTs catalyze the formation of mono(ADP-ribosyl)ation, but generally the attached ADP-riboses are built as polymers by PARPs, which are the most common ADP-ribosyltransferases [8]. PARP-1, one of five confirmed PARPs, is the most abundant and highly expressed nuclear enzymes widely involved in DNA-damage response, apoptosis, chromatin stabilization and epigenetic modifications in mammalians [82]. Overactivity of PARP-1 driven by DNA strand breaks or metabolic insults leads to NAD^+ exhaustion and bioenergetic failure [89] inducing caspase-independent apoptosis [106]. Indeed, this phenomenon was estimated to contribute for a 75 % depletion of NAD^+ [31]. Some pathogens were shown to take advantage of the loss of PARP-1 function to its own advantage. As example, *Chlamydia trachomatis* release a protease-like activity factor (CPAF) leading to the cleavage of PARP-1, assuring a reduced inflammatory response to membrane-damaged cells [104]. In opposition, PARP-1 activation was detected in the brains of Vietnamese patients with fatal *Plasmodium falciparum* malaria [52]. Interestingly, the use of PARP-1 inhibitor, 3-aminobenzamide, was protective against meningitis-associated central nervous system complications resulting from *Streptococcus pneumoniae* infection [43]. However, the role of PARP-1 in the integration of retroviral DNA and consequent steps of retroviral infections, as HIV and Moloney murine leukemia virus, remains controversial [2, 88]. Whereas some groups found that PARP-1 by decreasing the intracellular levels of NAD^+ in infected host cells contribute for the maintenance of infection [30], others report a viral transcriptional repression through epigenetic mechanisms [7].

The exacerbated activation of PARP-1 was shown to be associated with NAD^+ depletion, followed by the opening of mitochondrial permeability transition (MPT) pore [1]. In parallel, the disturbance of mitochondria homeostasis and the rupture of membrane potential cause mitochondrial and cellular NAD^+ depletion, culminating in cell death. Recently, the role of NAD^+ in different types of cell death has been vastly addressed [25]. The modulation of mitochondria damage by pathogens has also been demonstrated in several studies [55, 79]. Because mitochondria are also the primary site for reactive oxygen species (ROS) production, which constitute essential microbicidal molecules, it seems likely that NAD^+ modulation at the mitochondrial

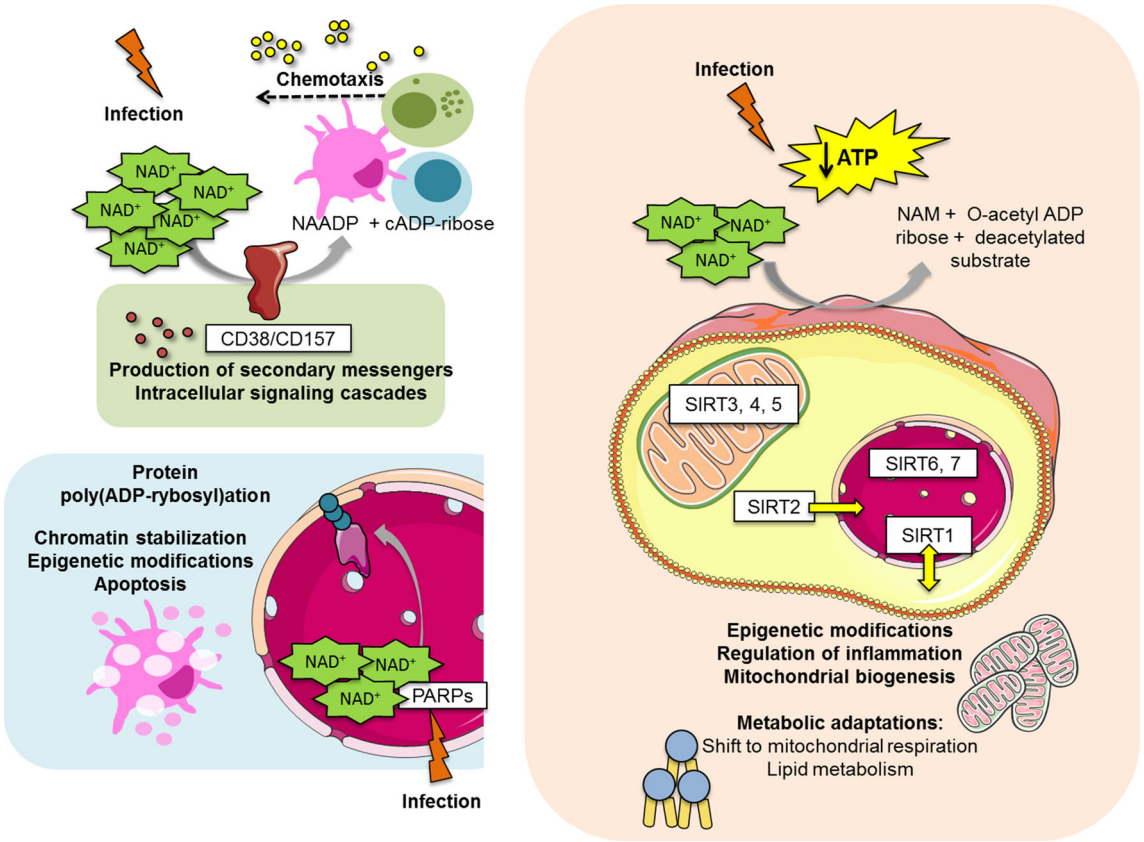

Fig. 2 Mechanistic action of NAD^+-consuming proteins during host–pathogen interaction. The three major classes of NAD^+-consuming proteins are involved in NAD^+ breakdown and utilization, which originates functional and metabolic alterations upon challenge. NAD^+ cleavage in NAADP and cADP-ribose is catalyzed by the ectoenzymes CD38 and CD157. When extracellular NAD^+ content is increased, a high NAD^+ turnover results in increased concentration of NAADP and cADP-ribose, which contribute for Ca^{2+} mobilization. This phenomenon leads to the production of secondary messengers, activation of intracellular signaling cascades and consequent chemotaxis of immune cells (for example, dendritic cells, monocytes and neutrophils) towards chemokine gradient. PARPs respond to DNA damage by infectious agents originating poly(ADP-rybosyl)ation of targeted proteins. This may have a role in chromatin stabilization and epigenetic modifications. Furthermore, PARP activation results in NAD^+ depletion and cell apoptosis due to decreased energy availability. The seven isoforms of sirtuins are spread in the nucleus (SIRT1, SIRT6 and SIRT7), the cytosol (SIRT2) and the mitochondria (SIRT3, SIRT4 and SIRT5), although SIRT1 may shuttle between the nuclear and cytosolic compartment and SIRT2 was already shown to be able to translocate to the nucleus. Upon sirtuin modulation by the presence of an infectious agent, NAD^+ is degraded and ultimately SIRT1 activity originates mitochondrial biogenesis and increased lipid oxidation. These processes lead to an increase of intracellular ATP levels, in an attempt to restore energy homeostasis. Sirtuins and PARPs are also able to cause epigenetic modifications in cellular DNA, which may also contribute to metabolism modulation. *ATP* adenosine triphosphate, *ADP* adenosine diphosphate, *cADP* cyclic adenosine diphosphate, *NAADP* nicotinic acid adenine dinucleotide phosphate, *NAD*$^+$ nicotinamide adenine dinucleotide, *SIRT* sirtuin, *PARP* poly-(ADP-ribose) polymerase

level may have an impact on microbe infections, but further studies are required.

Sirtuins

The mammalian sirtuin family comprises seven members, named SIRT1-7 [53], with distinct subcellular localizations reverting acetyl modifications of lysine residues or acting as ADP-rybosiltransferases in histones and other proteins. Sirtuins are activated in situations of energy deficit and prompt the utilization of non-carbohydrate energy sources, such as fatty acids [36]. The induced metabolic shift allows the organism to increase the efficiency of energy production.

SIRT1 was shown to be upregulated in hepatitis B virus (HBV) infected-liver cells. Its pharmacological inhibition by sirtinol was associated with a suppression of viral DNA replication, suggesting that SIRT1 inhibitors might be used as novel therapies to treat HBV infection [76]. The overexpression of hepatitis C virus (HCV) core proteins in HepG2 cells leads to an alteration in the cellular redox state, with decreased NAD^+/NADH ratio. This imbalance was suggested to derive from a decreased signaling in the SIRT1-AMPK pathway, contributing to the hepatic

metabolic disorder and influencing disease progression and anti-viral therapy efficacy [105]. Along the same line, Moreira and colleagues demonstrated the role of energy sensors AMPK and SIRT1 in *Leishmania* parasites survival and proliferation [56]. NAD^+/NADH fluctuations during the course of infection reflected a correlation between SIRT1 activity and host metabolism driving pathogen persistence. Conversely, SIRT1 knockdown or inhibition by NAM and sirtinol in Kaposi's Sarcoma-Associated Herpesvirus (KSHV)-infected cells resulted in increased concentration of infectious virions, which could reactivate the virus from the latent stage [32, 48]. Finally, the infection of human biliary epithelial cells with *Cryptosporidium parvum*, a coccidian parasite, resulted in higher SIRT1 expression, in a let-71-dependent manner that ultimately regulates NF-κB-driven innate immune response [101].

Interestingly, *Listeria monocytogenes* infection was impaired through H3K18 deacetylation-dependent fashion in SIRT2 knockout mice or blocking SIRT2 activity [23]. The role played by SIRT2 during infection appears to be pathogen-specific since the modulation of SIRT2 activity in vivo did not affect chronic infection with *M. tuberculosis* [11]. Therefore, it is critical to further explore the implications of sirtuin modulation during infections, especially since several sirtuin activators/inhibitors are in the biopharmaceutical pipeline to tackle metabolic, cardiovascular, neurodegenerative and neoplastic diseases.

The importance of NADP(H) in host–pathogen interactions

In contrast to NAD^+/NADH, the $NADP^+$/NADPH ratio must be maintained at very low levels. NADPH, the reduced form of $NADP^+$, is known to provide reducing equivalents for anabolic reactions, such as fatty acid biosynthesis. It is also vital for protecting cells against reactive oxygen species (ROS), produced notably by the mitochondrial metabolism, through its role as cofactor for NADPH-dependent glutathione reductases, which ultimately ensures the regeneration of reduced glutathione (GSH). During host–pathogens interactions, NADPH is further used as an electron donor for NADPH oxidases activation that play both effector and signalling roles in the course of infection, through generation of microbicidal ROS [34, 66, 96]. Seven NADPH oxidases isoforms have been characterized in humans; the five NOX enzymes produce superoxide anion, while the two Dual Oxidase enzymes (DUOX1-2) generate hydrogen peroxide in a Ca^{2+}-dependent manner (reviewed in [75]). NADPH oxidase NOX2, found in the membranes of neutrophils and macrophages phagosomes, has been extensively studied. During pathogen phagocytosis, this membrane-linked complex (composed of $gp91^{phox}$; $p22^{phox}$; $p47^{phox}$; $p40^{phox}$; $p67^{phox}$; and small GTPase Rac) associates, resulting in the oxidation of NADPH to $NADP^+$ with the concomitant production of superoxide ($O_2^{\cdot-}$) from oxygen and the remaining downstream ROS to eliminate invading pathogens [67]. DUOX 1 and 2 are expressed in the epithelial surfaces of salivary glands, airways and along the gastrointestinal tract. The initial evidences of the in vivo role of DUOX enzymes in the crosstalk gut-microbiota were first provided in a *Drosophila* gut infection model system. The knockdown of DUOX on flies was shown to severely increase the susceptibility to gut infections (reviewed in [41]). Accordingly, Ha et al. [29] demonstrated that DUOX activity is essential for the maintenance of homeostasis in the fly gut in an infectious context through the development of an oxidative burst that is capable of limiting microbial proliferation. The tight control of DUOX enzymes allows the host gut–microbe homeostasis by efficiently controlling infection while tolerating commensal microbes [28]. In this context, the differential sensing of gut microbiota by innate immune sensors (Nod and Toll-like receptors) as well as the activation of distinct signalling pathways (Myd88, TRIF or NF-κB) has been shown to play a critical role by controlling the expression and activity of DUOX enzymes [33, 90]. Similarly, DUOX-derived ROS has been demonstrated to be essential for the innate immune response against bacterial or viral infections in airway mucosa [37, 39, 49, 92]. Thus, DUOX enzymes work in close collaboration with innate immune recognition receptors to develop an efficient innate immune response to viral or bacterial pathogens [37, 39]. However, its role in controlling parasite infections has never been addressed.

The beneficial versus detrimental role of NADPH oxidase activation in infectious contexts has been recently addressed. While some pathogenic bacteria, viruses and parasites have developed different means to limit NADPH oxidase activation and escape oxidative burst [93, 96], others seem to use NADPH oxidase activation and ROS production for their own benefit [34, 66]. Moreover, this is not limited to phagocytic cells. NOX/DUOX enzymes in the lung epithelium has been shown to participate in the host defense against respiratory viruses [27]. In opposition, hepatic NOX proteins during chronic hepatitis C virus were associated with exacerbated oxidative stress that leads to hepatocellular carcinoma [15], while ROS-generating NOX5 are essential for HTLV-I virus mediated T cell transformation phenotype [86].

For pathogens, the maintenance of high levels of NADPH is considered fundamental for survival. If in one hand, the pathogens have to adapt to the oxidative burst naturally present in the phagosomes, on the other this

hostile environment may be aggravated by antiparasitic drugs act that act through generation of oxidative stress. Similarly to what happens in host cells, the majority of the antioxidant cofactor NADPH produced by parasites and bacteria derives from the concomitant action of G6PDH and 6PGD in the pentose phosphate pathway (PPP), which

Table 1 Pathogen-specific and host enzymes involved in host intracellular NAD^+ modulation during infectious diseases

Pathogen-specific enzymes	Pathogen	Observations	References
Nicotinamidase	*Leishmania* spp.	Maintenance of parasite homeostasis and infectivity	[26]
	Brucella abortus	Contribution for intracellular replication and infectivity	[40]
	Borrelia burgdorferi		[40]
NAD^+ glycohydrolase	Group A streptococci	Depletes intracellular NAD^+ and ATP	[3, 13, 54, 64, 95]
NadN	*Haemophilus influenzae*	NAD^+ synthesis from NMR and NR by NadN	[38, 44, 87]
NadA	*Shigella* spp.	NAD^+ synthesis from quinolinate and aspartate by NadA and NadB	[72]
NadB			[73]
Pathogen's homolog enzymes			
PfNMNAT	*Plasmodium* spp.	Inhibition of PfNMNAT: parasite growth arrest	[63]
NAD^+ synthase	*Mycobacterium tuberculosis*	De novo and salvage synthesis using NAD^+ synthase	[99]
Host enzyme modulation			
IDO/TDO	*Staphylococcus aureus*	Induction of IDO by IFNy: inhibition of replication	[83]
	Mycobacterium tuberculosis	Starving of tryptophan: bacteria elimination	[108]
	Toxoplasma gondii	Blockage of IDO: attenuation of *T. gondii* replication	[60]
	Clostridium difficile	IDO KO mice: increased pathology	[22]
	LP-BM5 murine leukemia virus	IDO inhibition: suppression of virus replication via type I IFN	[35]
	HIV	Induction of IDO: dysfunction of CD8 T cells; shift Th22 to Tregs	[4, 16]
	Hepatitis B virus	Infection up-regulates IDO expression	[81]
	Hepatitis C virus		[81]
	Influenza virus		[81]
NAMPT	HIV	NAMPT induction: prevents proviral DNA integration	[14, 97]
	Plasmodium spp.	NAMPT induction: increased NAD^+ levels in infected erythrocytes	[107]
	Staphylococcus aureus	Inhibition of NAMPT: decreased inflammation	[78]
CD38	*Streptococcus pneumoniae*	CD38 KO mice: more susceptible to infection	[68]
	Mycobacterium avium		[98]
	Entamoeba histolytica	CD38 KO mice: decreased protozoa elimination	[24]
	Naegleria fowleri	CD38 KO mice: loss of ability to induce inflammatory response	[12]
PARP	*Chlamydia trachomatis*	Cleavage of PARP-1 by secreted protease-like activity factor	[104]
	Plasmodium falciparum	PARP-1 activation in patients with fatal malaria	[52]
	Streptococcus pneumoniae	PARP-1 inhibitor: protective against meningitis	[43]
	HIV	Controversial role for PARP-1	[2, 7, 30, 88]
Sirtuins	Hepatitis B virus	SIRT1: upregulated in infection; sirtinol: protective	[76]
	Hepatitis C virus	Imbalanced SIRT1/AMPK axis: hepatic disorder	[105]
	Leishmania infantum	Activation of the SIRT1/AMPK axis contributes	[56]
	Kaposi's Sarcoma-Associated Herpesvirus	SIRT1 knockdown or inhibition: increase in infectious virions	[32, 48]
	Cryptosporidium parvum	Increased expression of SIRT1	[101]
	Listeria monocytogenes	SIRT2 knockdown or inhibition: impairment of infection	[23]
	Mycobacterium tuberculosis	SIRT2 knockdown: no impairment in chronic infection	[11]

makes this metabolism an attractive target for weakening of pathogen's defenses. G6PDH deficiency is one of the most common enzymopathy found in humans, affecting over 400 million people. This genetic disorder is more frequent in Africa and it mostly affects red blood cells (RBC) that are unable to produce sufficient NADPH levels and become therefore highly susceptible to oxidative stress. Paradoxically, G6PDH-deficient persons are more resistant to *Plasmodium* infections in Africa. The possible explanations are that chronic oxidative stress generated in G6PDH-deficient infected RBCs limit infection by *Plasmodium* or that these RBCs cannot sustain a normal infection and will be rapidly eliminated by macrophages [10, 59]. All these examples underline a complex role of NADPH in host/pathogen interactions, with both a role in the generation and the resistance to produced ROS during infection.

Concluding remarks

The biosynthetic pathways that culminate with NAD^+ production are currently being used to fight non-infectious diseases, demonstrating its importance in novel drug design [3, 9, 57, 80]. It is possible to draw an analogy of this principle for infectious diseases. The remaining outstanding questions are: (1) Would it be more efficient to target host and/or pathogens NAD^+ metabolism? (2) Upon blockage of a biosynthetic enzyme and consequent NAD^+ depletion, are the pathogens able to evade elimination by upregulating other enzymes or by retrieving NAD^+ from other sources? (3) Will the targeting of such an important molecule affect not only the host infected cells, but also bystander or non-infected cells? A rapid and considerable drop in NAD^+ levels may cause massive cell death. More importantly, do the pathogen's enzymes differ significantly, in terms of homology, from host's ones, allowing its specific target? Or should the therapeutic approaches focus only in pathogen-specific and unique enzymes, as the nicotinamidases? It is also important to acknowledge the importance of maintaining NAD^+ levels for the activation of metabolic sensors, as the sirtuins, and downstream signaling pathways. The correct functioning of host cells depends on the intricate connection between processes that drive cell survival, proliferation and host defense. The modulation of NAD^+ levels is predicted to affect effector functions of immune cells and, consequently, the clearance or persistence of infections. Therefore, the study of NAD^+ biology may be a promising approach for the discovery of new targets against infectious diseases. Table 1 synthetizes the major mechanisms used by pathogens to modulate host NAD^+ levels. Remarkably, the first trials targeting NAD^+ biology in infectious diseases go back to 1945, where nicotinamide was explored as an anti-*M. tuberculosis* agent, and later on during the 1990's as an anti-HIV drug [61]. Although all of this information had fallen into obscurity, the past decade has seen the renaissance of targeting NAD^+ biology to tackle infectious diseases, which has been accompanied by the arrival of new structure-based chemical modulators [6, 65, 74, 80, 94]. Nonetheless, the investigation of NAD^+ metabolome is taking its first steps and it is expected to convey important updates regarding the interface between metabolism and immunity.

Acknowledgments JG was supported by PD/BD/106053/2015. BV was supported by IRD (Institut de Recherche pour le Développement) institutional funding. JE was supported by a European Community's Seventh Framework Program under grant agreement No. 602773 (Project KINDRED), an ANR grant (LEISH-APO, France) and a Partenariat Hubert Curien (PHC) (program Volubilis, MA/11/262). JE also thanks the Canada Research Chair program for his support. RS thank FCT—Foundation for Science and Technology—for their Investigator FCT Grant (IF/00021/2014)

Compliance with ethical standards

Conflict of interest The authors have declared that no competing interests exist.

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