Chapter 4
Alterations on Cellular Redox States upon Infection and Implications for Host Cell Homeostasis

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Abstract The cofactors nicotinamide adenine dinucleotide (NAD^+) and its phosphate form, $NADP^+$, are crucial molecules present in all living cells. The delicate balance between the oxidized and reduced forms of these molecules is tightly regulated by intracellular metabolism assuring the maintenance of homeostatic conditions, which are essential for cell survival and proliferation. A recent cluster of data has highlighted the importance of the intracellular NAD^+/NADH and $NADP^+$/NADPH ratios during host–pathogen interactions, as fluctuations in the levels of these cofactors and in precursors' bioavailability may condition host response and, therefore, pathogen persistence or elimination. Furthermore, an increasing interest has been given towards how pathogens are capable of hijacking host cell proteins in their own advantage and, consequently, alter cellular redox states and immune function. Here, we review the basic principles behind biosynthesis and subcellular compartmentalization of NAD^+ and $NADP^+$, as well as the importance of these cofactors during infection, with a special emphasis on pathogen-driven modulation of host NAD^+/$NADP^+$ levels and contribution to the associated immune response.

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

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R. Silvestre, E. Torrado (eds.), *Metabolic Interaction in Infection*, Experientia Supplementum 109, https://doi.org/10.1007/978-3-319-74932-7_4

4.1 Introduction

The maintenance of an adequate cellular redox state, characterized by a tight regulation of the intracellular levels of nicotinamide adenine dinucleotide (NAD^+) and its phosphate form, $NADP^+$, is a vital premise for cellular homeostasis. NAD^+ is reduced to NADH during catabolic reactions, which yields a high quantity of mitochondrial respiration-driven energy to fulfil cellular needs. NADPH is regenerated from $NADP^+$ through a variety of redox reactions that support reductive biosynthesis contributing to maintain the cellular pool of reduced glutathione (GSH), essential for the development of detoxification mechanisms. Consistent with these important roles in cell biology, the intracellular NAD^+/NADH and $NADP^+$/NADPH ratios have arisen as central players in metabolic homeostasis, as well as cell survival and proliferation. A growing body of evidences has begun to unravel the importance of NAD^+ and $NADP^+$ bioavailability and fluctuations during host-pathogen interactions. In this chapter, we will revisit the alterations on cellular redox states and further implications for host cell homeostasis and defence against distinct infectious agents and argue for NAD^+ and $NADP^+$ metabolism as potential therapeutic targets.

4.2 The Biosynthetic Machinery Behind NAD^+ and $NADP^+$ Production

In eukaryotic cells, NAD^+ is originated either through de novo synthesis or by salvage pathways. The de novo pathway relies on the uptake and metabolism of dietary L-tryptophan in N-formylkynurenine, a rate-limiting step catalysed by indoleamine 2,3-dioxygenase (IDO) or tryptophan 2,3-dioxygenase (TDO). Following subsequent enzymatic reactions, quinolinic acid is generated and converted in nicotinic acid mononucleotide (NaMN), which then originates nicotinic acid adenine dinucleotide (NaAD), through the action of nicotinamide mononucleotide adenylyltransferases (NMNATs 1–3). The final step in de novo synthesis is the conversion of NaAD in NAD^+ by the glutamine-dependent NAD^+ synthase (Magni 2008). However, NAD^+ pools can also be replenished through salvage pathways, which rely on the uptake of biosynthetic precursors, namely, nicotinic acid (NA), nicotinamide (NAM) or nicotinamide riboside (NR). Both these biosynthetic pathways may converge by activation of the Preiss–Handler pathway, in which NA is converted to NaMN by the NA phosphoribosyltransferase (NAPT). Additionally, NAM can originate NAD^+ via NAM mononucleotide (NMN) intermediate, through the combined action of the rate-limiting NAM phosphoribosyltransferase (NAMPT) and NMNAT (Revollo et al. 2007). Finally, NR can also be phosphorylated in NMN by nicotinamide ribose kinase (NRK) and then adenylated to NAD^+ by NMNAT (Fig. 4.1).

The conversion of NAD^+ to $NADP^+$ allows the cells to sustain a high demand in reducing equivalents, such as in conditions where high levels of nucleotide, protein

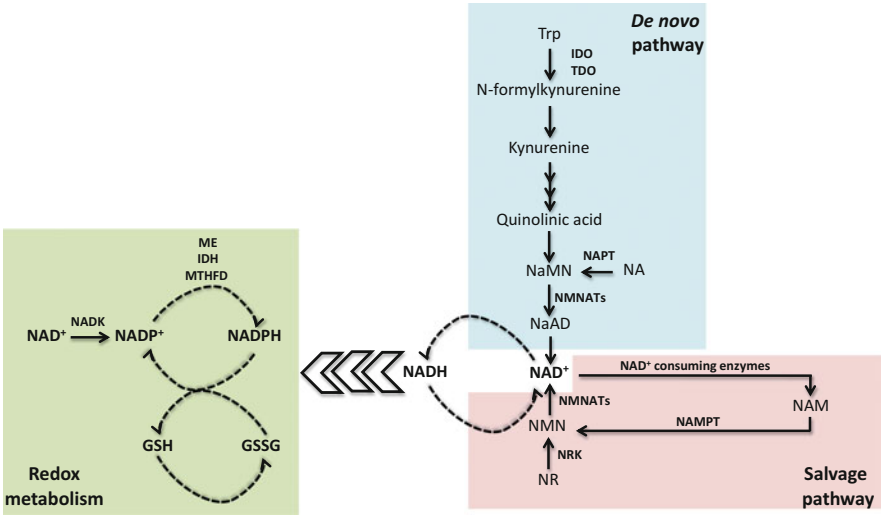

Fig. 4.1 Intracellular machinery for $NAD^+/NADP^+$ synthesis in mammals. De novo (blue) and salvage (red) pathways for NAD^+ production, as well as $NADP^+$ production and utilization during redox metabolism (green) are depicted. *GSSG* oxidized glutathione, *GSH* reduced glutathione, *IDH* isocitrate dehydrogenase, *IDO* indoleamine 2,3-dioxygenase, *ME* malic enzyme, *MTHFD* methylene tetrahydrofolate dehydrogenase, *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

and lipid synthesis, or detoxification mechanisms are required. The only known enzyme responsible for this replenishment through NAD^+ phosphorylation is NAD^+ kinase (NADK). NADPH regeneration may be achieved in the cytosol and/or mitochondria through the activity of several enzymes: glucose-6-phosphate dehydrogenase (G6PDH) and 6-phosphogluconate dehydrogenase in the oxidative branch of pentose phosphate pathway (PPP), methylenetetrahydrofolate dehydrogenase (MTHFD) and aldehyde dehydrogenases (ALDHs) during folate metabolism and isocitrate dehydrogenases (IDHs) and malic enzyme (ME) in the tricarboxylic acid (TCA) cycle.

The use of ^{13}C-labelled tracers has helped to address the metabolic activity during cellular events. However, using this technology to address NADPH biosynthesis may originate misleading data, as the same carbon source may originate both NADH or NADPH, depending on the isoenzyme involved: some enzymes that catalyse NADPH synthesis, as MTHFD, ALDHs and IDHs may also generate NADH (Liu et al. 2016; Tibbetts and Appling 2010; Wise et al. 2011).

4.3 Intracellular Pools of NAD^+ and $NADP^+$

As abovementioned, adequate ratios of these cofactors within the intracellular milieu must be maintained to guarantee the development of adequate metabolic functions. The exquisite balance between the reduced and oxidized forms of these cofactors depends on the cellular requirements and the chosen metabolic pathways that will fulfil them. On one hand, NAD^+ catalyses catabolic reactions, as it is used as a hydrogen acceptor in several steps of the TCA cycle. During these dehydrogenation reactions, NADH is produced, and the majority of newly synthetized molecules are redirected to oxidative phosphorylation, in an attempt to produce high quantities of adenosine triphosphate (ATP). On the other hand, cytosolic NADPH production relies greatly on the oxidative branch of the PPP, as well as serine-driven one-carbon metabolism (Fan et al. 2014). Upon production, this cofactor is essentially used in biosynthetic pathways that require a strong reductive power (as lipid synthesis) and cellular detoxification mechanisms. Furthermore, a layer of complexity is added when considering that cellular membranes are not permissive to the flow of numerous molecules and that these cofactors are not only essential in the cytosol but are also key elements within distinct organelles. As so, cells are capable of preserving compartmentalized and independent pools, as in the case of NAD^+ (Dölle et al. 2010). Interestingly, intracellular $NADP^+$ content is somewhat limiting, when considering the vast number of metabolic pathways that rely on the bioavailability of this cofactor (proliferation, lipid synthesis and defence against stressful conditions). Similar to what happens with NAD^+, $NADP^+$ is also compartmentalized in different organelles, and electron transport across membranes is only achieved through shuttles. Accordingly, in eukaryotic cells, metabolic reactions can take place in different organelles that will condition and impact the further utilization of specific metabolites and precursors. Consequently, a cluster of studies has started to highlight the importance of certain pathways in the replenishment of organelle-specific pools of NAD^+ and $NADP^+$.

4.3.1 Subcellular NAD^+ Compartmentalization

The main cellular pools of NAD^+ are the cytosolic and mitochondrial ones (VanLinden et al. 2015), with the cytosolic being around 100 times superior than the mitochondrial counterpart. It is estimated that while the cytosolic pool displays NAD^+/NADH ratios between 60 and 700, the mitochondrial one ranges from 7 to 8 (Williamson et al. 1967). Considering the need for distinct intermediates and cofactors during different metabolic processes, it is well-defined the importance of NAD^+ compartmentalization when considering the impermeability of cellular membranes. One of the main enzymes responsible for this subcellular specificity and control of NAD^+ pool distribution is the biosynthetic enzyme NMNAT, which has three distinctly localized isoforms: NMNAT1 is a nuclear enzyme, NMNAT2 has a cytosolic localization and

NMNAT3 is present at the mitochondria (Mori et al. 2014). It is known that the isoform 1 is the most efficient enzyme, responsible for adenylyl transference or pyrophosphorylysis and for the maintenance of the nuclear NAD^+ pool. However, whether NMNAT1-driven NAD^+ can shuttle to the cytoplasm, by exchange through nuclear pores, is still questionable, as cytosolic NAD^+ may be replenished through NMNAT2 activity. The mitochondrial NAD^+ pool is maintained by NMNAT3 (Lau et al. 2010; Di Stefano and Conforti 2013), which is the enzyme with lowest selectivity for purine nucleotides, and it appears to be independent of other enzymes in the NAD^+ biosynthetic pathway as NAMPT inhibition by FK866 does not affect NAD^+ intramitochondrial levels (Pittelli et al. 2010). The maintenance of individually compartmentalized regions is essential for preventing short-term cell death in the event of massive NAD^+ depletion. This protective capacity, mainly mediated by the activation of a SIRT3/SIRT4/NAMPT-mediated axis, is known as the 'mitochondrial oasis effect', during which cell viability is maintained for a short period of time after cytosolic NAD^+ depletion, due to the preservation of mitochondrial function (Yang et al. 2007).

4.3.2 Subcellular $NADP^+$ Compartmentalization

One of the most important characteristics associated with eukaryotic cell metabolism is the compartmentalization of metabolic reactions within organelles. Similar to what happens with NAD^+, multistep shuttles are used to transfer NADPH-reducing power between the different cellular compartments to ensure correct organellar metabolic processes. The use of isotope tracing experiments has provided new insights regarding cytosolic and mitochondrial production of NADPH, namely, the contribution of the PPP for cytosolic pools and serine/glycine metabolism for the mitochondrial one. The major source of NADPH production is the oxidative branch of PPP in the presence of a high demand of nucleotide synthesis. As abovementioned, other potential sources of cytosolic NADPH include reactions catalysed by IDH, malic enzyme (ME), ALDH and MTHFD (Pollak et al. 2007; Tibbetts and Appling 2010). However, some isoforms of these enzymes are involved in mitochondrial reactions, which may explain the transference of reducing equivalents between cytosol and mitochondria. For instances, IDH2 catalyses the reductive carboxylation of alpha-ketoglutarate (αKG) to isocitrate in the mitochondria, at the expense of one molecule of mitochondrial NADPH. Next, citrate/isocitrate may be shuttled to the cytosolic compartment, where it is oxidized by IDH1, with a concomitant production of cytosolic NADPH (Wise et al. 2011). ME is a $NADP^+$-dependent enzyme, which through malate decarboxylation generates NADPH to fuel fatty acid synthesis, the most NADPH-demanding pathway in eukaryotes. The three isoforms (1, 2 and 3) are distinctively compartmentalized (ME1 is cytosolic, while ME2 and ME3 are mitochondrial), thus contributing for separate pools of NADPH. Lewis et al. (2014) have recently developed a reporter system that allows the tracing of compartmentalized sources of NADPH. In this work, they took advantage of a neomorphic mutant IDH,

which catalyses the conversion of αKG into (*D*)2-hydroxyglutarate (2HG), through transference of a hydride from NADPH. The production of 2HG serves as an end-product readout, as this metabolite is not further metabolized. By supplementing the cells with [3-^{2}H]-glucose and assessing the enrichment of ^{2}H in the 2HG pool, the authors were able to discriminate between mitochondrial versus cytosolic NADPH production. Furthermore and considering that serine and glycine interconversion generates NADPH, Lewis et al. sought to evaluate the contribution of this metabolic pathway in NADPH compartmentalization, thus showing that serine metabolism is capable of replenishing mitochondrial NADPH. Mitochondrial NADPH may also be produced through activity of a nicotinamide nucleotide transhydrogenase (NNT), which transfers reducing equivalents from NADH to NADPH (Gameiro et al. 2013). This purely cofactor-modulating enzyme has been shown to modulate central carbon metabolism, namely, through coordination of glucose and glutamine metabolism in the TCA cycle, as NNT knockdown affected glucose and glutamine consumption in cancer cell lines.

4.4 The Role of NAD^{+} and NADP^{+} During Host–Pathogen Interactions

As abovementioned, the maintenance of homeostatic levels of both NAD^{+} and NADP^{+} is essential for a correct cellular function that supports survival and proliferation. This is particularly important when acknowledging that, upon infection, the metabolic requirements of host cells are altered, in order to privilege certain pathways to fulfil their highly demanding cellular needs. This suggests that the bioavailability of certain precursors within the intracellular milieu is essential in dictating if a host cell is capable of arresting or sustaining the infectious process, which will ultimately allow for the pathogen to be cleared or to thrive and persist within the host. When considering the importance of adequate NAD^{+}/NADH and NADP^{+}/NADPH ratios in the establishment of an appropriate metabolic environment, it seems clear that fluctuations in these factors or in the bioavailability of their building blocks impact host defence and pathogen success. In fact, it has already been demonstrated the importance of NAD^{+} and NADP^{+} levels during infection and how these ratios may be altered upon pathogen proliferation (Mesquita et al. 2016).

4.4.1 Pathogen-Driven Modulation of NAD^{+} Levels

Several reports have shown how the modulation of host NAD^{+} levels is imperious for achieving effective pathogen colonization and survival. However, additional layers of complexity arise when considering that distinct cell types and pathogenic agents may drive different alterations in host cell energy status. For instance, upon

erythrocyte infection, the parasitic agent *Plasmodium falciparum* increases the intracellular levels of NAD^+, which is due to increased activity of NAMPT and NAPT (Zerez et al. 1990). The observed elevation of NAD^+ levels is expected to be essential for supporting a high glycolytic rate in the infected erythrocyte, which displays a concomitant upregulation of lactate production (Olszewski et al. 2009). Conversely, human immunodeficiency virus (HIV) infection of human peripheral blood lymphocytes (PBMCs) leads to a decrease in intracellular NAD^+ levels (Murray et al. 1995). Having in consideration that advanced states of HIV infection display common features with pellagra (a clinical state that is associated with niacin deficiency), it was also shown that exogenous administration of NAM inhibits HIV replication in PBMCs (Murray and Srinivasan 1995). Consistent with these findings, it has been recently suggested that a disruption of host metabolic machinery by HIV (and also other viruses) may contribute to persistence of the HIV reservoir and, consequently, disease and pathogenesis progression (Palmer et al. 2016). Infection of macrophages with the protozoan agent *Leishmania infantum* was shown to induce a transient increase in NAD^+ levels, 18–24 h postinfection, which is consistent with a metabolic switch towards mitochondrial respiration at later stages of infection (Moreira et al. 2015).

Group A streptococci (GAS) has a noteworthy capacity of modulating NAD^+ levels in infected cells. Among other virulence factors, GAS produce a NAD^+ glycohydrolase that cleaves NAD^+ to produce NAM, adenosine diphosphate (ADP)-ribose and cyclic ADP-ribose (Tatsuno et al. 2010). Along with streptolysin O, these virulence factors promote intracellular survival within host cells, mainly by preventing phagolysosome acidification and thus evading the immune system (Bastiat-Sempe et al. 2014; Sharma et al. 2016). In a mechanistic perspective, it was shown that NAD^+ glycohydrolase depletes intracellular NAD^+ and ATP levels (Michos et al. 2006), which disrupts several host defence mechanisms and contributes to dissemination and chronic persistence. Moreover, NAD^+ glycohydrolase expression also protects against xenophagic killing, thus allowing for increased bacterial survival in pharyngeal keratinocytes (O'Seaghdha and Wessels 2013). In an experimental model of pneumococcal meningitis, it was demonstrated that an activation of the kynurenine pathway and consequent accumulation of 3-hydroxykynurenine in the hippocampus were correlated with extended apoptotic damage (Bellac et al. 2006). Consistently, it was also shown that pharmacological inhibition of 3-hydroxylase and kynureninase leads to a decreased level of NAD^+, thus originating energy failure and consequent cell death. These data seem to suggest that the replenishment of cellular NAD^+ pools during infection may serve as a neuroprotective mechanism (Bellac et al. 2010).

Recent evidences have also suggested the link between liver X receptor (LXR) pathway and NAD^+ intracellular metabolism during macrophage infection with invasive bacteria. Matalonga et al. (2017) proposed that LXR activation originates a reduction of intracellular NAD^+ levels, through a CD38-dependent mechanism. This activation decreased macrophage bacterial burden, due to alterations in cytoskeleton dynamics. Additionally, exogenous administration of NAD^+ rescued the infective ability of the bacteria. Furthermore, using an in vivo model of infection with *Salmonella* Typhimurium, an amelioration of the clinical symptoms and

protection against bacteria dissemination upon treatment with LXR agonists was also observed, which emphasizes the relevance of LXR agonists or other inducers of CD38 NADase activity as potential therapies against infection.

Despite all these recent examples showing that infection with intracellular pathogens can directly increase or decrease host NAD^+ levels, further studies are required to determine the druggability of this metabolism for therapeutic intervention.

4.4.2 The Impact of Enzymes Involved in NAD^+ Metabolism in Host Immune Response Towards Invading Pathogens

4.4.2.1 Indoleamine 2,3-Dioxygenase

The most well-studied enzyme in NAD^+ de novo synthesis is IDO, which catalyses the rate-limiting step in tryptophan catabolism and, consequently, contributes to tryptophan depletion. More than a metabolic hub of amino acid metabolism, this enzyme has arisen as an important regulator of immune plasticity and homeostasis, particularly during autoimmunity, infection and neoplasia. It has been shown, using different models, that IDO has an immunosuppressive role, characterized by an impairment of effector T cell proliferation and induction of regulatory T cells (Prendergast et al. 2014). During tryptophan starvation, naïve $CD4^+$ T cells become tolerogenic, and autoimmune-preventive T regulatory cells are generated, through a general control nonderepressible 2 (GCN2)-dependent mechanism (Fallarino et al. 2006). In opposition, IDO activity may also be controlled by interferons, which are major players in the development of an immune response. This crosstalk between tryptophan catabolism and immune modulation indicates IDO as a major metabolic rheostat, which suggests that it may be involved in host immune response towards invading pathogens.

It has been shown in distinct infectious models that genetic or pharmacological modulation of IDO alters infection outcome (Munn and Mellor 2013; Schmidt and Schultze 2014). Furthermore, considering that several important human pathogens are tryptophan auxotrophs, it is expected that IDO-mediated depletion of this metabolite may further influence microorganism survival (Brown et al. 2008). IDO has already been demonstrated to be essential for gut homeostasis and development of a protective response against bacteria and other pathogens. Consistently, in a context of experimental colitis, IDO inhibition resulted in higher mortality, when compared with the placebo-treated animals, as well as increased immunopathology and elevated colonic pro-inflammatory cytokine expression (Gurtner et al. 2003). Furthermore, using a *Clostridium difficile* infection model, IDO knockout mice displayed increased mucosal destruction and caecal haemorrhage, along with increased levels of interferon (IFN)-γ-producing neutrophils (El-Zaatari et al. 2014). This phenotype appears to indicate that tryptophan catabolism may be a central mechanism associated with the regulation of tissue pathology and control of bacterial burden.

Several research groups addressed the role of IDO during HIV infection. This chronic infection is characterized by a progressive and severe immune dysfunction, associated with increased tryptophan metabolism by IDO (denominated as *tryptophan starvation*). The induction of this enzyme is driven by host- and virus-derived factors, such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4)/B7 engagement; IFN-α and IFN-γ production by the innate and adaptive immune system, respectively; and HIV-associated proteins (Boasso et al. 2007). The immunosuppressive role of IDO is mainly correlated with its capacity to impair CD4 and CD8 T cells (Boasso et al. 2007, 2008), which results in the gradual establishment of a state of T cell anergy, characteristic of HIV infection. Additionally, Potula and colleagues showed that IDO inhibition by the competitive inhibitor 1-methyl-tryptophan (1-MT) increases cytotoxic CD8 T cells and decreases HIV-infected macrophages in a murine model of HIV encephalitis (Potula et al. 2005). In line with the already described importance of IDO during HIV infection, Vujkovic-Cvijin et al. showed that during both acute and chronic simian immunodeficiency virus (SIV) infection of rhesus macaques, a specific depletion of gut-resident *Lactobacillus* is correlated with increased levels of IDO1 and loss of T helper (Th)17 cell abundance. The observed phenotype suggests that IDO1 inhibition by *Lactobacillus* species may serve as a protective mechanism that prevents Th17 loss (Vujkovic-Cvijin et al. 2015). Consequently, the maintenance of gut homeostasis may prevent microbial translocation into the bloodstream, which is a hallmark of chronic immune activation and disease progression in HIV patients.

Other viral infections have been associated with induction of IDO expression in immune cells. A lipooligosaccharide expressed by the pathogenic agent of chancroid, *Haemophilus ducreyi*, is responsible for IDO induction in dendritic cells, via type I interferon- and tumour necrosis factor (TNF)-α-dependent mechanisms, as well as modulation of the mitogen-associated protein kinase (MAPK), nuclear factor kappa B (NF-κB) and Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathways (Li et al. 2011). In a similar fashion, IDO expression was also increased during macrophage infection with Epstein-Barr virus (EBV), which is commonly associated with infectious mononucleosis and human malignancies. Furthermore, EBV-induced IDO expression was linked to an impairment of the cytotoxic activity of CD8 T cells, which are vital for the control of viral particles, as well as cancer progression (Liu et al. 2014). West Nile virus induces IDO expression on infected macrophages through a NF-κB-dependent manner. Although IDO is not required for the control of flavivirus replication, its expression prior to macrophage exposure to West Nile virus prevents infection (Yeung et al. 2012). These results suggest that, although IDO is commonly associated with immune suppression and dysfunction, its impact during infection may be time-dependent, as well as pathogen-dependent.

Although IDO has a very noteworthy role during host-pathogen interactions, other enzymes involved in NAD^+ anabolism and catabolism may be associated with host susceptibility versus resistance during infection.

4.4.2.2 Nicotinamide Phosphoribosyltransferase

NAMPT, a biosynthetic enzyme from the salvage pathway, inhibits HIV replication in monocytes by preventing the integration of proviral DNA in host genome (Van den Bergh et al. 2010). However, a multifunctional transactivator encoded by HIV, the Tat protein, is capable of inhibiting NAMPT activity and consequently depleting intracellular NAD^+ pools. Consistently, an imbalance in NAD^+ content in the intracellular milieu further impacts the activity of NAD^+-consuming protein, as sirtuin (SIRT)1 (Zhang et al. 2010). The inhibition of SIRT1 activation during HIV infection has been associated to Tat-induced p53 activation and decreased deacetylation of SIRT1 (Thakur et al. 2012). Pretreatment of HeLa-CD4-long terminal repeat (LTR)-β-gal (MAGI) cells transfected with Tat plasmid with resveratrol, a natural product that activates SIRT1, resulted in increased NAD^+ levels and attenuates Tat-induced HIV transactivation (Zhang et al. 2010). Furthermore, pretreatment with SIRT1 inhibitor, nicotinamide, results in the opposite phenotype, which indicates that SIRT1 inhibition by Tat is crucial for an adequate viral proliferation (Zhang et al. 2009). Another natural compound, tanshinone II A, has been shown to inhibit Tat-regulated HIV transactivation. After treatment of TZM-bl cells with tanshinone II A, SIRT1 and NAMPT activity is rescued, as well as intracellular NAD^+ levels. Furthermore, the increase in NAMPT expression appears to result from activation of adenosine monophosphate-activated protein kinase (AMPK) signalling pathway (Zhang et al. 2014).

This cluster of data insinuates that this important link between the regulation of NAD^+ levels and viral replication can be used in the development of new therapeutic strategies against HIV infection, with a particular emphasis towards the NAMPT/SIRT1 axis. It is important to emphasize that alterations in NAD^+/NADH levels, driven by changes in anabolic versus catabolic mechanisms, are also associated with metabolic disorders and altered cellular functions, as seen, for instance, during sepsis. Sepsis is potentially life-threatening complication, derived from a generalized bacterial or fungal infection, which is associated to an acute inflammatory response and eventually a late immunosuppressive state. It has been recently shown that cellular bioenergetics is essential in dictating the functional fate of immune cells, which are rendered tolerant upon septic shock. Using an in vitro model of immunotolerance, Chen et al. demonstrated that immunotolerant monocytes, when restimulated with lipopolysaccharide (LPS), showed a defect in glucose fermentation, characterized by decreased production of lactate and NAD^+ levels, when compared with non-tolerant ones. Furthermore, LPS-stimulated PBMCs from immunotolerant patients with sepsis displayed a similar defective phenotype, which was only restored upon patient recovery from septic shock (Cheng et al. 2016). The shift from an acute to a late inflammatory stage during sepsis is associated with a switch from a glycolytic phenotype, highly dependent on NAD^+ availability, to an oxidative metabolism, characterized by fatty acid oxidation. It was demonstrated that during Toll-like receptor (TLR) 4 stimulation, this switch is coordinated by a crosstalk between NAMPT, SIRT1 and SIRT6: while NAMPT drives NAD^+ production to allow a metabolic coupling between the acute and late

stage on inflammation, NAD^+-dependent SIRT1 and SIRT6 coordinate the increase in fatty acid oxidation and decrease in glucose fermentation, thus integrating the metabolic reprogramming with the immune response during sepsis (Liu et al. 2012). Furthermore, during the phase of cellular adaptation to sepsis, it was shown that the sequential activity of NAD^+-dependent SIRT1 and mitochondrial SIRT3 is essential in driving a functional mitochondrial biogenesis (Liu et al. 2015). This suggests that NAD^+ availability is essential in dictating the outcome after septic shock, as well as the metabolic reprogramming during endotoxin tolerance, such as the activity of several proteins, like sirtuins, are highly dependent on intracellular NAD^+ pools.

4.4.2.3 NAD^+-Consuming Proteins

NAD^+ is a vital cofactor for three distinct classes of proteins: sirtuins, poly(ADP-ribose) polymerases (PARPs) and CD38/157, where it serves as a donor of ADP-ribose and, therefore, controls the levels of extracellular and intracellular NAD^+. These nucleotide-metabolizing proteins are *metabolic sensors*, responsible for the tight regulation of energy metabolism, cell survival and proliferation.

CD38/157 Membrane Proteins

The class of cADP-ribose synthases, also known as the lymphocyte antigens CD38 and CD157, are involved in the production of secondary messengers that play important roles in distinct signalling pathways. These proteins are the main regulators of NAD^+ levels, as around 100 molecules of NAD^+ require processing to yield a single molecule of cADP-ribose (Dousa et al. 1996; de Toledo et al. 2000). As membrane proteins, these molecules possess an extracellular domain, and its rapid activity is responsible for maintaining low levels of extracellular NAD^+ (Seman et al. 2004). Consistently, during homeostasis, low quantities of NAD^+ are found in mice serum (Kim et al. 1993). However, upon infection or tissue damage, NAD^+ levels can quickly rise and be secreted. This extracellular NAD^+ activates $P2Y_{11}$ purinoceptors at the surface of human granulocytes, which contributes for their functional activation (Moreschi et al. 2006). Following CD38 activation, Ca^{2+} levels are dramatically increased, which promotes the migration of innate immune cells (as monocytes, neutrophils and dendritic cells) to danger sites and to secondary lymphoid organs (Partidá-Sánchez et al. 2007). The role of CD38 in the regulation of immune responses has already started to be elucidated in vivo, by taking advantage of $CD38^{-/-}$ mice. Partida-Sánchez et al. (2001) showed that in the absence of these proteins, mice become more susceptible to *Streptococcus pneumonia*, as neutrophils appear to be incapable of accumulating in the lung of infected animals and are irresponsive to the bacterial chemoattractant fMLP. Likewise, using an experimental infection with *Listeria monocytogenes*, Lischke et al. (2013) showed that the absence of CD38 renders the mice more susceptible 3 days postinfection, which

suggests a role of this molecule in the innate immune response. $CD38^{-/-}$ mice also display higher susceptibility to *Mycobacterium avium* infection, as Th1 differentiation and polarization seem to be impaired. Furthermore, alterations in the granulomatous barrier were also observed in these animals, which suggest that the absence of CD38 promotes bacterial dissemination and growth (Viegas et al. 2007). Likewise, $CD38^{-/-}$ mice display a reduced hepatic elimination of *Entamoeba histolytica*, which is associated with a limited inflammatory response (Estrada-Figueroa et al. 2011).

This cluster of data suggests that a deeper understanding of the role of CD38 and extracellular NAD^+ levels is essential for achieving a specific modulation of the inflammatory responses, with the aim of better controlling the infectious process.

PARPs

Mono- or poly(ADP-ribosyl)ation (PARylation) reactions, which are mediated by ADP-ribose transferases (ARTs) or PARPs, are also dependent on NAD^+ availability. PARP-1 is the most abundantly expressed protein of the PARP family, and it is involved in DNA damage response, cell death by apoptosis and epigenetic alterations in mammalian cells (Schreiber et al. 2006). This protein induces the translocation of ADP-ribose molecules from NAD^+ to acceptor proteins or to a previously formed poly(ADP-ribose) chain. In situations of PARP-1 overactivity, which may be driven by metabolic insults, intracellular NAD^+ pools are depleted, and the cell enters in a state of bioenergetic failure, which culminates with the initiation of the apoptotic pathway (Sodhi et al. 2010; Yu et al. 2002). During infection, some pathogens may hijack host PARP-1 activity in their own advantage. Recently, it was demonstrated that PARP-1 is overexpressed in *Helicobacter pylori*-infected gastric mucosa and that antibiotic treatment reduces gastric inflammation, through decreasing PARP-1 expression and NF-kB activation (Lee et al. 2016). In EBV-infected B cells, pharmacological inhibition, as well as genetic ablation of PARP-1 suppressed the expression of latent membrane protein (LMP) 1-activated genes, which are essential for driving EBV latency and tumorigenesis (Martin et al. 2016). Consistently with this report, a recent study highlighted the role of PARP-1 in the inhibition of EBV lytic reactivation, through binding at the *BZLF1* lytic switch promoter. Furthermore, EBV reactivation has a negative impact on PARP-1 activity, which reinforces the restrictive function of this molecule towards EBV reactivation (Lupey-Green et al. 2017). In a very similar fashion, it was demonstrated that Kaposi's sarcoma-associated herpesvirus (KSHV) also downregulates PARP-1 upon reactivation. This is due to the expression of viral processivity factor of KSHV (PF-8), which directly interacts with PARP-1 and triggers proteasome-dependent degradation (Cheong et al. 2015). In line with these data, Navarro et al. developed a mouse model that exhibited PARP-1-deficiency with a *Cd4*-promoter-driven conditional deletion of PARP-2 in T cells. Mice bearing a double deficiency in PARP-1 and -2 displayed an accumulation of DNA damage, which conditioned the replenishment of the memory pool in response to vaccinia virus infection (Navarro et al. 2017). The role of PARP-1 during HIV infection

has been vastly studied; however, it has also suffered immense debate: several contradictory reports suggest that PARP-1 activation is essential for HIV DNA integration (Ha et al. 2001; Kameoka et al. 2005), while other state that it is not only dispensable (Siva and Bushman 2002), but also associated with an impairment of the viral process (Gutierrez et al. 2016; Rom et al. 2015). This suggests that further studies are required to understand the exact impact of PARP-1 activity during viral infections.

The activity of PARP-1 has also been addressed during bacterial infections, although at lower extent. Following *Mycobacteria* infection of alveolar macrophages, necrosis appears to be induced as a possible evasion strategy that allows infectious bacteria to escape and disseminate to new host cells. Wu and colleagues showed that, upon Bacillus Calmette-Guerin (BCG) infection of RAW264.7 macrophages, NAD^+ levels are decreased, which is consistent with an increase in PARP-1 expression. Furthermore, they demonstrated that activation of Wnt/β-catenin signalling prevents BCG-induced macrophage necrosis, which appears to be correlated with increased levels of intracellular glutathione and downregulation of PARP-1 expression (Wu et al. 2015). Similarly, PARP-1 activation was found in the brainstem of patients that died with *Plasmodium falciparum* malaria (Medana et al. 2001). PARP-1 inhibition with 3-aminobenzamide was shown to attenuate NAD^+ depletion and pneumococci-induced cytotoxicity, in a context of experimental pneumococcal meningitis (Koedel et al. 2002). Using a lipopolysaccharide-induced model of acute lung injury, it was demonstrated that PARP-1 inhibitor, 3, 4-Dihydro-5[4-(1-piperindinyl) butoxy]-1(2H)-isoquinoline, reduced lung inflammation and vascular leakage, as well as neutrophil infiltration and the establishment of an inflammatory environment, thus promoting a protective phenotype (Wang et al. 2013).

These reports suggest that the modulation of PARP-1 activity may be explored in the context of potential therapies against infections. However, it is necessary to have in consideration that alterations in PARP-1 activity may be cell- and context-specific, so each individual case should be properly addressed.

Sirtuins

As abovementioned, sirtuins are a class of NAD^+-dependent proteins, and this family of proteins includes seven members (SIRT1-7), which display distinct subcellular localizations (Michan and Sinclair 2007). Sirtuins are activated in situations of energy deficit and, therefore, prompt metabolic shifts to increase ATP production, namely, through utilization of noncarbohydrate energy sources, as fatty acids (Houtkooper et al. 2012).

It was recently shown that SIRT1 is downregulated during in vitro *Mycobacterium tuberculosis* (Mtb) infection of monocytes/macrophages and the rescue of SIRT1 activation during the course of infection leads to dampened inflammatory responses, through deacetylation of RelA/p65 and impaired binding to the promoter of inflammatory genes. Furthermore, in *Mtb*-infected mice, SIRT1 activators improved lung pathology, decreased inflammatory responses and augmented the efficacy of anti-TB drugs (Cheng et al. 2017). This suggests that SIRT1 activators may disclose a

potential utilization during host-directed therapies for the treatment of tuberculosis. Similarly, treatment of *Trypanosoma cruzi*-infected mice with SIRT1 agonists, resveratrol or SRT1720, decreased cardiac pathology and improved heart function in chagasic mice (Wan et al. 2016). In line with this, it was shown that SIRT1 knockdown or inhibition by NAD^+ precursor NAM or sirtinol in KSHV-infected cells originated an increase in the quantity of infectious virions (He and Gao 2014; Li et al. 2014). Ganesan and colleagues showed that macrophage infection with virulent *Salmonella enterica* serovar Typhimurium is characterized by a quick drop in ATP and NAD^+ levels, which originated a transient activation of AMPK. This metabolic sensor appears to be regulated by the complex liver kinase B1 (LKB1)/SIRT1, which is degraded in lysosomes, culminating in the disruption of AMPK-derived modulation of mammalian target of rapamycin (mTOR). This suggests that *S. Typhimurium* degrades host cell proteins as an evasion strategy to avoid xenophagy and consequent bacterial elimination (Ganesan et al. 2017). Interestingly, during macrophage infection with the protozoan parasite *Leishmania infantum*, Moreira et al. observed a metabolic switch towards a respiratory phenotype, which was consistent with AMPK activation 10–14 h postinfection. Furthermore, the increase in NAD^+ levels of 18 h postinfection was concomitant with the observed decrease in SIRT1 expression, which suggests that *L. infantum* is capable of modulating host SIRT1 activity by altering the redox status of the host cell (Moreira et al. 2015). Likewise, the parasite *Cryptosporidium parvum* is also capable of altering SIRT1 expression, as infected human biliary epithelial cells display higher levels of SIRT1, which regulates NF-kB-driven innate immune response (Xie et al. 2014). SIRT1 expression was also found to be increased during hepatitis B virus (HBV) infection, with its inhibition by sirtinol being associated with a suppression of viral replication (Ren et al. 2014).

Although SIRT1 is the most studied member of the sirtuin family, some reports regarding the role of the other members during infections have started to appear, namely, SIRT2. Upon *L. monocytogenes* infection, SIRT2 is translocated to the nucleus, where it deacetylates histone H3 on lysine 18 (H3K18) and possibly reprogrammes host cells to allow bacterial proliferation. Consistently, experimental infection of $SIRT2^{-/-}$ mice resulted in an impairment in bacterial proliferation, which suggests that SIRT2-mediated H3K18 deacetylation has an essential role during *L. monocytogenes* infection (Eskandarian et al. 2013). However, the role of this protein during infection is most likely pathogen-specific, as the modulation of SIRT2 during *Mtb* infection did not alter the outcome of chronic infection (Cardoso et al. 2015).

Although sirtuins have recently arisen as very promising drug targets for metabolic, neurodegenerative, cardiovascular and neoplastic diseases, it is wise to further study their implication during infectious processes, especially when considering their possible modulation by invading pathogens. The major mechanisms of action of NAD^+-consuming proteins and metabolic consequences during host–pathogen interaction is synthetized on Fig. 4.2.

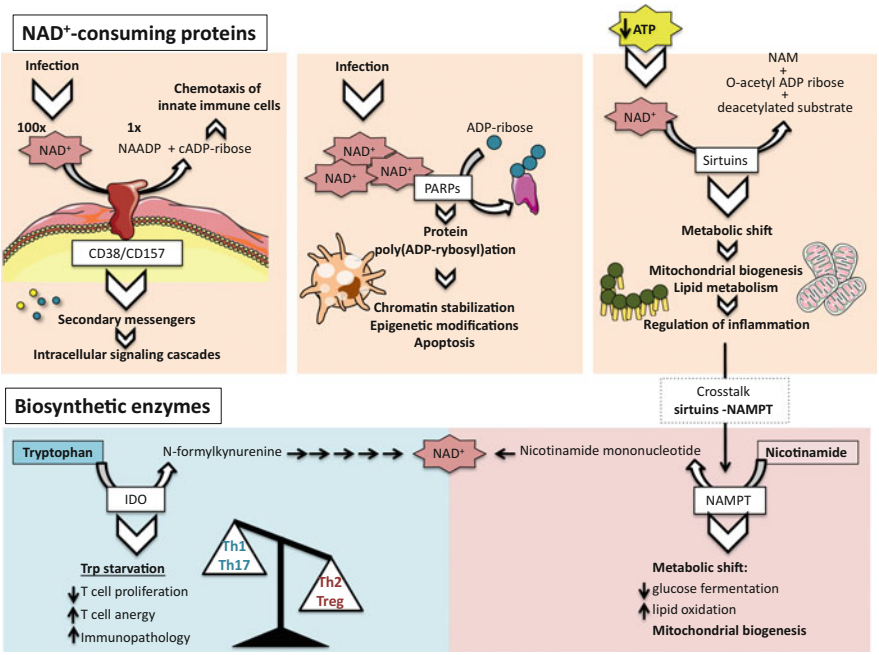

Fig. 4.2 Mechanism of action of NAD^+-consuming proteins and metabolic consequences during host–pathogen interaction. Three major classes of NAD^+-consuming proteins are involved in NAD^+ catabolism upon infection: CD38/157, PARPs and sirtuins. The ectoenzymes CD38/157 are responsible for the breakdown of 100 molecules of NAD^+, with concomitant production of one molecule of NAADP and cADP-ribose, which are involved in the activation of intracellular signalling pathways and in the chemotactic process of innate immune cells, such as neutrophils, dendritic cells and monocytes, to the sites of inflammation. PARPs respond to DNA damage with a simultaneous poly (ADP-rybosyl)ation of target protein, which may be at the genesis of epigenetic alterations. The consequent NAD^+ depletion may reduce intracellular energy reservoirs and induce apoptotic cell death. Sirtuins (SIRT1-7) may be modulated by energy stress associated with the infectious process. Upon activation, sirtuins degrade NAD^+ and originate a metabolic shift that aims at restoring energetic homeostasis, with a possible function in regulating inflammation. Biosynthetic enzymes, such as IDO and NAMPT, may be targeted by pathogens and consequently alter intracellular NAD^+ levels. Tryptophan starvation, originated by hyperactivation of IDO, originated an unbalance in T cell response, characterized by anergy and a decrease in pro-inflammatory subsets, such as Th1 and Th17. Activation of NAMPT during infection may also originate a metabolic switch towards an oxidative phenotype, which is most likely connected with sirtuin activity and function. *ADP* adenosine diphosphate, *ATP* adenosine triphosphate, *IDO* indoleamine 2,3-dioxygenase, *NAD^+* nicotinamide adenine dinucleotide, *NAADP* nicotinic acid dinucleotide phosphate, *NAMPT* nicotinamide phosphoribosyltransferase, *PARPs* poly(ADP-ribose) polymerases, *Th* T helper, *Trp* tryptophan

4.5 Pathogen-Driven Modulation of $NADP^+$ Levels

NADPH can provide reducing equivalents for anabolic processes, as fatty acid synthesis, and to protect cells against oxidative burst-induced damage. It acts as a cofactor for NADPH-dependent glutathione reductases that yield reduced glutathione,

essential for detoxifying reactive oxygen species (ROS), mainly formed in the mitochondria. The NOX family of NADPH oxidase is the major source of ROS during host–pathogen interactions. These transmembrane proteins are capable of crossing electrons through biological membranes and consequently produce superoxide or hydrogen peroxide from oxygen reduction. These microbicidal ROS are detrimental to pathogen survival, and, therefore, it is hypothesized that the maintenance of redox potential through NADPH regeneration is vital for host defence against intracellular microbes (Van Assche et al. 2011; Hogan and Wheeler 2014; Paiva and Bozza 2014). In humans, NADPH oxidases display seven isoforms, responsible for the production of distinct types of ROS in different tissues. NOX1-5 are responsible for the production of superoxide anion, while the two dual oxidase enzymes (DUOX1-2) produce hydrogen peroxide (Rada and Leto 2008). The most well-characterized isoform is NOX2, which is found in macrophage phagosomes and in neutrophil membranes. NOX2 possesses six distinct subunits ($gp91^{phox}$, $p22^{phox}$, $p47^{phox}$, $p40^{phox}$, $p67^{phox}$ and Rac GTPase) that, upon activation by pathogen phagocytosis, interact to form an active complex that oxidizes NADPH to $NADP^+$. Once activated, this complex fuses with the plasma or phagosomal membrane and transfers the electrons to oxygen yields superoxide, which aims at eliminating the invading pathogen and protecting the host cell (Panday et al. 2015). Upon phagocytosis, different evasion mechanisms may be adopted by the pathogens to circumvent killing by ROS, namely, through subversion of the respiratory burst or by phagosome escape. However, recent studies have challenged this paradigm by demonstrating that some antioxidants can be used as therapeutic agents against certain pathogens (Mittal et al. 2014). Furthermore, exacerbated ROS levels may induce tissue damage and increased pathological inflammation, which may be detrimental for the host.

DUOX1 and 2 are mainly expressed in mucosa-associated epithelium, as the surface of salivary glands, airways and the gastrointestinal tract. The role of these enzymes was initially described using a *Drosophila* model, where a knockdown of DUOX rendered the flies more sensitive to gut infections (Kim and Lee 2014). This susceptible phenotype was partially attributed to alterations in gut homeostasis as well as decreased oxidative burst and, consequently, increased pathogen proliferation (Ha 2005). DUOX2 expression may be regulated by NOX1 activity during intestinal infection with *Citrobacter rodentium*. Accordingly, Cyba ($p22^{phox}$) deficiency, which inactivates NOX 1–4, was shown to protect against gut infections. This was mediated by activation of a compensatory mechanism in which gut commensals rescue impaired hydrogen peroxide production, which negatively regulates *C. rodentium* virulence factors (Pircalabioru et al. 2016).

One of the most studied mechanisms associated with host defence is the development of an adequate respiratory burst, during which several types of ROS contribute to pathogen clearance. Consistently, an impairment in the establishment of a hostile microenvironment may contribute to pathogen thriving. Chronic granulomatous disease (CGD) is a primary immunodeficiency caused by mutations in any of the five genes (*CYBB*, *CYBA*, *NCF1*, *NCF2* and *NCF4*) that encode for components of the phagocyte NADPH oxidase complex. It is essentially characterized by an impairment of intracellular pathogens killing, due to a lack of NADPH oxidase-derived ROS. Due to this defect, CGD patients develop aggressive forms of bacterial and fungal infections, as well as dysregulated inflammatory responses

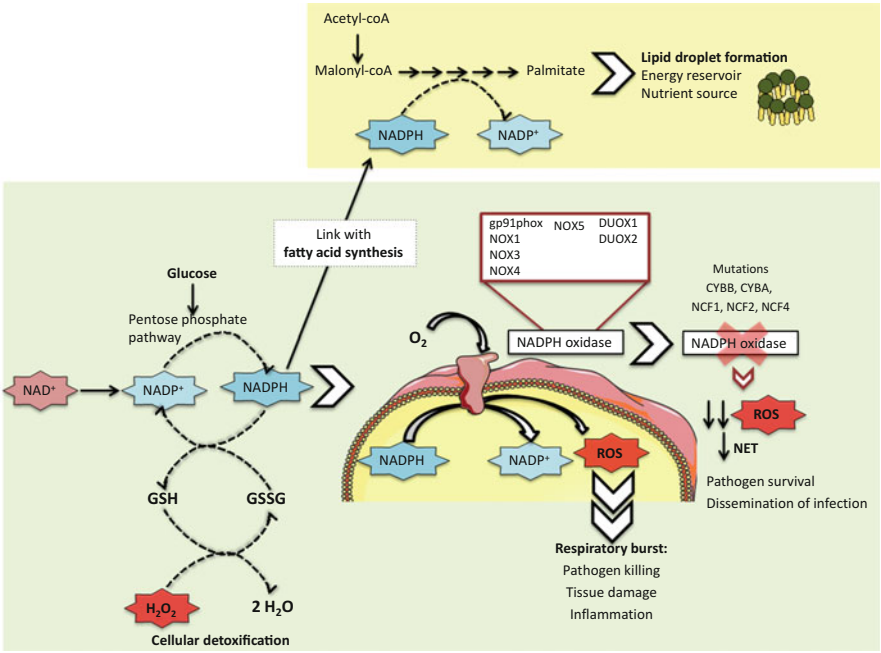

Fig. 4.3 $NADP^+$/NADPH metabolism and function in host cell metabolism, homeostasis and defence mechanisms. $NADP^+$ may be obtained through phosphorylation of NAD^+. The major contributor for intracellular $NADP^+$ pools is the pentose phosphate pathway. NADPH may be spent to regenerate GSH, which is used for cellular detoxification of ROS. NADPH oxidases (gp91phox, NOX1, NOX3, NOX4, NOX5, DUOX1, DUOX2) are responsible for the production of microbicidal ROS (respiratory burst), at the expense of NADPH molecules. Mutations in different subunits of the NOX family of NADPH oxidases (*CYBB*, *CYBA*, *NCF1*, *NCF2*, *NCF4* genes) originate decreased levels of ROS, which downregulates host cell microbicidal mechanisms and allow pathogen survival and dissemination. NADPH may equally be used during fatty acid synthesis, thus contributing for an increased pool of intracellular lipid droplets. *GSSG* oxidized glutathione, *GSH* reduced glutathione, *NAD^+* nicotinamide adenine dinucleotide, *$NADP^+$* nicotinamide adenine dinucleotide phosphate, *NET* neutrophil extracellular trap, *ROS* reactive oxygen species

being particularly susceptible to mycobacteriosis and aspergillosis (Conti et al. 2016; Deffert et al. 2014; Segal and Romani 2009). The available treatment for the comorbidities linked to this disease poses a challenge, particularly when having in consideration that the majority of immunomodulators can exponentiate the degree of immune suppression already observed in these patients. Recently, the utilization of gene therapy as a curative treatment of this primary immunodeficiency has been suggested, namely, for the treatment of fungal infections (Grez et al. 2011). During CGD, the defects in NADPH oxidase originate decreased pathogen killing, since there is a downregulation in the production of neutrophil extracellular traps (NETs), which is highly dependent of ROS production. Consequently, *Aspergillus* hyphae can infect and disseminate. The restoration of NETs formation by gene therapy results in increased ability to control aspergillosis (Bianchi et al. 2009), in a process driven by calprotectin released by NETs, which prevented spreading of fungal components (Bianchi et al. 2011; Fig. 4.3).

As previously mentioned, cellular detoxification depends mainly on reduced NADPH mainly assured by the action of G6PDH in the PPP. A deficiency in this enzyme, which is highly prevalent in the African population, results in a defect in controlling reactive oxygen species and, therefore, increased oxidative stress. A clear example of the intricate complexity associated with NADPH in host–pathogen interactions is the reduced susceptibility of G6PDH-deficient people to *Plasmodium falciparum* infection (Uyoga et al. 2015). Although these individuals are more susceptible to oxidative stress, *Plasmodium* parasites are unable to establish a successful infection. Eventually, infected red blood cells are eliminated by macrophages, thus clearing the pathogen (Müller 2004).

4.6 Concluding Remarks

The study of NAD^+ and $NADP^+$ biology has highlighted the possibility of using the acquired knowledge in the development of new therapeutic strategies during infection. The modulation of the intracellular levels of these cofactors appears to be a requisite for the adequate establishment of a pathogen within host cells. However, several outstanding questions are still to be answered: (1) Would counteracting the observed modulation of $NAD(P)^+$/NAD(P)H be an effective strategy to tackle infection? (2) After modulation of biosynthetic pathways, are pathogens capable to bypass the altered intracellular milieu and thrive within the host cell? (3) Can pathogen auxotrophy be the driving force behind evasion mechanisms? (4) Is it possible to target $NAD(P)^+$/NAD(P)H metabolism in infected cells, without compromising the homeostasis of both uninfected and bystander cells? Although it seems clear that $NAD(P)^+$/NAD(P)H metabolism is a central hub during infectious diseases, further studies are mandatory to understand how we can effectively modulate these pathways. Additionally, it is important to acknowledge that the majority of the studies where the role of these cofactors during host–pathogen interactions was elucidated lack the intrinsic complexity of living beings, and notably the fluctuations in NAD^+ biosynthesis related to the circadian clock (Peek et al. 2013). Targeting $NAD(P)^+$/NAD(P)H biology during an experimental in vitro infection is vital for understanding the underlying cellular and molecular mechanisms associated with resistance versus susceptibility. However, transposing this knowledge for clinical therapy may be a challenging and a long-lasting protocol. Nonetheless, important steps towards the utilization of $NAD(P)^+$/NAD(P)H biology to fight infectious diseases have been made, and the following years will be crucial for developing new strategies.

Funding Statement This work was supported by the Northern Portugal Regional Operational Programme (NORTE 2020), under the Portugal 2020 Partnership Agreement, through the European Regional Development Fund (FEDER) (NORTE-01-0145-FEDER-000013) and the Fundação para a Ciência e Tecnologia (FCT) (contracts SFRH/BD/120127/2016 to IM and IF/00021/2014 to RS), and Infect-Era (project INLEISH).

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