# Roles of Nox3 in Diseases

Reactive oxygen species (ROS) were formerly known as mere byproducts of metabolism with damaging effects on cellular structures. The discovery and description of NADPH oxidases (Nox) as a whole enzyme family that only produce this harmful group of molecules was surprising. Among the Nox isoforms, the NADPH oxidase 3 is the perhaps most underrated Nox enzyme, since it was firstly discovered in the inner ear. Despite the fact that Nox3 is expressed not only in the inner ear but also in various cell types and organs, the "inner ear stigma" remains until today. However ,the involvment of Nox3 is not just limited to the inner ear but extends to various organs and the related diseases.

1. Role of Nox3 in Hearing Loss

Hearing loss affects one out of six people and it is one of the major common sensory impairments of humans worldwide [1][2][3]. Hearing loss can be caused by various extrinsic and intrinsic factors, i.e., noise exposure, drug application (including cisplatin), infections and age-related degeneration [3][4][5][6]. The hearing loss in general results from compromised functioning of the organ of Corti in the cochlea and/or the nerve pathways connected to the auditory part of the brain [7]. Several research studies have reported that the nerve connection from the auditory system of the brain to the sound detecting cells (i.e., the hair cells) of the organ of Corti are the most vulnerable parts damaged by endogenous or exogenous sources [8][9][10][11]. The organ of Corti is built up from IHCs and OHCs surrounded by inner and outer phalangeal cells (or Deiters' cells), inner and outer pillar cells, Hensens cells and Claudius' cells, all summed up under the term "supporting cells" [12] (**Figure 1**A). The hair cells detect low- or high-frequency sounds in dependency on their position [13]. Sensory hair cells, in general, do not regenerate in mammals [14][15] and continuous damage results in the permanent loss of hair cells [16]. Oxidative distress is a major driver of hair cell death and subsequent cochlear damage [4][17][18][19][20][21][22][23], which can be induced alongside noise [24][25][26][27], antibiotics [28][29][30], ototoxic anticancer drugs [28][31], infection [32][33] and aging [22][23][34][35][36]. Theses exogenous or endogenous stress factors all result in increased metabolic activity of the cochlea and increased ROS production [26][37][38]. In some cases, like low blood pressure and/or oxygen deprivation, ROS production waves were measured, which started at the luminal surface of the marginal cells in the stria vascularis [39] and re-occurred after reperfusion of the cochlea. The increased ROS levels can last for a long period of time, for example, up to 10 days after noise exposure [37][38][40][41]. This continuous oxidative distress ultimately contributes to death of OHCs and spiral ganglion cells [42][43][44], irreversible cochlea damage and, tragically, permanent hearing loss [8][45][46]. There are many ROS sources in cells with mitochondria [47][48][49] and Nox enzymes as the most prominent ones [50][51][52]. Importantly, mitochondria of OHCs increase their respiratory activity after noise exposure and generate increased amounts of ROS as byproduct [17][53][54], which also contribute to the harmful oxidative damage besides Nox enzymes in general and Nox3 in particular. I point to various excellent reviews about ROS in the inner ear [55][56] or Nox enzymes in this context [22][57] and focus on Nox3-derived ROS. Notably, many studies have used in vivo Wistar rat models, whose hearing ranges are from around 200 Hertz (Hz) to 90 kHz [58] and measured auditory brainstem responses (ABR) for determining the hearing capacity as major experimental output [59][60].
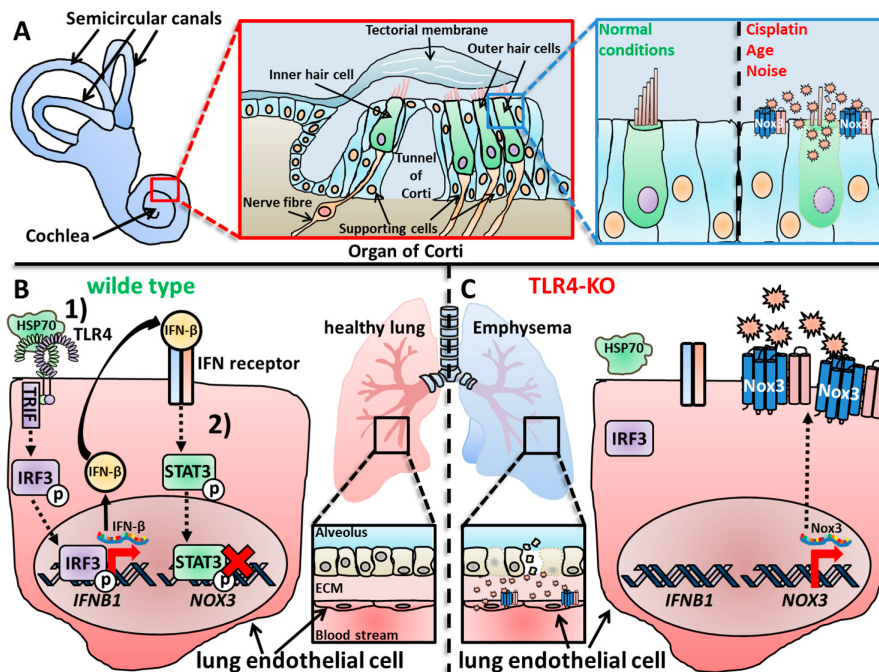
Figure 1. Overproduction of ROS or ROS production in the wrong location can lead to oxidative distress, cellular damage, malfunctioning of tissues and organs and finally manifest in diseases. (**A**) The cochlea is the organ responsible for hearing and in contrast to the vestibular system, loss of Nox3 leads to a rather protective outcome for the tissue and the hearing capacity. In the cochlea, the organ of Corti is responsible for detection of sound waves and neuronal processing. For that, outer and inner hair cells detect movements of the tectorial membrane, which are induced by incoming sound waves. Under healthy conditions, hair cells and supporting cells function normally; however, under exogenous or endogenous stress conditions, supporting cells up-regulate Nox3. The subsequent ROS overproduction leads to hair cell death and contributes to age-, noise- and drug-induced hearing loss [59][61][62]. (**B**) In WT mice, the development of lung emphysemas with increasing age is inhibited by a complicated signaling cascade in lung endothelial cells [63][64]. (**1**) Heat shock protein 70 (Hsp70) activates Toll-like receptor 4 (TLR4)-mediated signaling, which finally leads to activation and translocation of the transcription factor Interferon regulatory factor 3 (IFR3) into the nucleus. IFR3 induces the expression and production of Interferon-β (IFN-β), which is subsequently secreted and (**2**) activates the lung cells via binding to the IFN receptor in an autocrine manner. The IFN receptor-induced signaling cascade results in activation and translocation of the transcription factor Signal transducer and activator of transcription 3 (STAT3), which then binds to the promoter of the *NOX3* gene in result inhibiting the expression of Nox3. (**C**) In TLR4-deficient animals, this autocrine signaling cascade does not activate, which leads to increased mRNA expression and synthesis of Nox3 and subsequently to an increased ROS production of lung endothelial cells. The accumulating oxidative damage results in destruction of the alveolar structures and subsequently to the development of lung emphysemas in TLR4-deficient mice observed with increasing age.

Nagamani et al. first reported a correlation of four patients with interstitial deletion in the 6q region of the long arm of chromosome 6 and Nox3 expression [65]. Deletions of the 6q region were reported before to be associated with ear anomalies [66][67][68][69], but hearing loss was rarely reported [70]. The study suggested that hearing loss occurred because of interstitial or terminal deletions in the 6q25 region, precisely between the regions 6q25.2 and 6q25.3. This area harbors 12 protein-coding genes, with the *NOX3* gene among them. The study described for the first time a possible involvement of Nox3-related inner ear diseases in humans, which started the investigation of Nox3 as harmful ROS source and possible therapeutic target (Section 6) for patients.

1.1. Noise-Induced Ototoxicity

Prolonged exposure to noise is the most common cause of hearing loss worldwide [71][72][73][74][75][76] responsible for 20% of all cases of hearing loss [6]. Exposure to sound pressure levels that exceed 85 dB or immediate exposure to noise impulses lead to irreversible cochlea damage. Exposure to moderate sound levels over a prolonged time period can also harm the spiral ganglion neurons [77][78]. Noise-induced hearing loss is a result from the combined damaging effects of synaptic damage and cochlear hair cell death [79][80]. The noise-induced hearing loss can be temporary or permanent in dependency of the duration, severity and combination of the damaging factors [8]. A number of additional factors can worsen the progress of hearing loss, e.g., other diseases [81][82], social [17][83] and work behavior [84][85] or working conditions [86]. The frequency ranges of the impairment lie between 3.4 and 6 kHz [86]. Previous studies have also suggested genetic components, which might influence the outcome and severity of noise-induced hearing loss [87][88]. For

example, mice that already showed age-induced hearing loss were more susceptible to additional noise-induced hearing loss [89]. Furthermore, several mouse lines, which were deficient for antioxidant components, such as superoxide dismutase 1 (SOD1) [38], glutathione peroxidase 1(GPX1) [38], plasma membrane calcium ATPase 2(PMCA2) [90] or Cadherin Related 23 (CDH23) [91] showed also increased sensitivity to noise-induced hearing loss. These findings suggest an important role for ROS in this context in general. Accordingly, a previous study from Ramkumar et al. reported that noise exposure resulted in an increase of ROS levels, oxidative distress and increased pro-inflammatory responses in the chinchilla cochlea [92]. The pro-inflammatory status in the cochlea is mainly attributed to infiltrating immune cells, mainly monocytes [93][94][95], which respond to the cochlear tissue damage and the previously released chemokines from cochlear cells. Together with the already increased ROS production by Nox3 and mitochondria, the pro-inflammatory environment induces a vicious cycle that further increases the cochlear damage instead of dampening it [24][95][96][97]. Importantly, this pro-inflammatory, pro-oxidative setting is not restricted to noise-induced ototoxicity but can be applied to any effect that leads to increased ROS production and cochlear tissue damage. This scenario represents a complex network of cellular mechanisms and communication in the cochlea that still is incompletely understood and needs further investigation [98].

A number of studies performed genetic screens to identify possible factors that might contribute to noise-induced hearing loss. Lavinsky et al. used a well-established Hybrid Mouse Diversity Panel [99][100][101] to investigate possible loci for susceptibility towards noise-induced hearing loss [102]. The *Nox3^het* allele on the murine chromosome 17 was identified as candidate factor. *Nox3^het* mice were exposed to noise and ABR threshold shifts (4, 8, 12, 16, 24 and 32 kHz) were analyzed. The group measured a reduction in the ABR threshold shifts of WT mice in comparison to *Nox3^het* mice at 8 kHz suggesting a role for Nox3 during noise-induced hearing loss in the lower frequency spectrum. Zhao and colleagues performed a genome wide association study (GWAS) in 614 patients of a case-control study to investigate the interplay of noise kurtosis and lifestyle factors with noise-induced hearing loss [103]. Complex noise induces greater damage to the auditory system than steady noise in both animals and humans [104][105]. A complex noise is defined as continuous background noise with temporal appearance of randomly occurring high-level noises [106]. By transforming time-domain variables, like pulse interval distribution or duration, into simple variables by kurtosis [107][108][109], this experimental approach allows to assess the biological effects of complex noise in animal models [104][105][108]. The group reported that the risk of acquiring noise-induced hearing loss was 0.806-times higher for people, which were exposed to complex noise, as shown previously [105][108]. They detected an increased Guanine-to-Tyrosine polymorphism (single nucleotide polymorphism [SNP] rs12195525, GG phenotype) in the locus, which is located in the coding region of the *NOX3* gene. They also observed an increased risk for noise-induced hearing loss in GG phenotype patient groups in which further risk factors, such as smoking or high-volume outputs of technical devices, occurred.

The first study that connected the several correlative dots, i.e., Nox3 expression in the cochlea, per se [110], genetic correlations of noise-induced hearing loss with Nox3 [102][103], increased ROS levels in the cochlea as damaging factors [4][17][18][19][22][23], induction of ROS production by noise exposure [26][37][38] and the subsequent hearing loss, was conducted by Mohri and colleagues [59]. The group investigated the role of Nox3 during noise-induced hearing loss in their dtTomato-Cre reporter system for Nox3 detection in mice [59]. The group exposed 2-month-old WT and Nox3-deficient mice (Nox3 marked with the dtTomato fluorescence tag) to harmful noise at 120 dB for three hours and analyzed the ABR thresholds. At day 7, a lower ABR threshold shift at a high frequency (32 kHz) was measured in Nox3-deficient mice in comparison to WT animals. This was accompanied by a reduced OHC loss in Nox3-deficent animals directly linking Nox3 as damaging factor to hearing loss during noise exposure. A recent study from Rousset and colleagues revised previous findings [59][102] concerning the role of Nox3-derived ROS during hearing loss after white noise exposure [62]. Rousset et al. used the previously described C57BL/6J-*NOX3^het−4J* mouse strain [111], which carries a loss-of-function allele of Nox3. They applied RNAscope in situ hybridization on murine cochlea explants and detected strong Nox3 mRNA expression in the spiral ganglion, while Nox3 was only weakly expressed in the stria vascularis and not detectable in the organ of Corti. The latter is contradictory to several previous studies [59][110][112][113]. Additionally, they detected Nox3 mRNA in the peripheral auditory neurons in Rosenthal's canal. After noise exposure, Nox3 mRNA expression was increased in cochlear explants, precisely in the medial and the apical cochlea turns. The group also analyzed the hearing capacities of Nox3-deficient mice and observed no difference in the audiograms in comparison to WT animals after 6 weeks of age confirming not a general deficit of hearing in Nox3-deficient animals. Deafening noise exposure (116 dB) led to an elevation of hearing thresholds at frequencies between 16 and 32 kHz after 24 h in WT mice. A protective effect in Nox3-deficient animals was only observed for 32 kHz. After 7 days of noise exposure, ABR measurements showed a better recovery of hearing in Nox3-deficient mice, while WT animals showed no recovery. Histological examinations of cochlear explants further showed that Nox3-deficient animals had reduced hair cells loss, conserved auditory synapses and intact neuron integrity, which all were deceased in WT animals. This study nicely confirmed previous results [8][59][61][114][115], showing that Nox3 has no direct role for cochlear development and structures in sharp contrast to the otoconia formation in the vestibular

system [116][117][118]. Even worse, after noise exposure, Nox3-mediated ROS overproduction results in increased oxidative distress and damage of cochlear structures (**Figure 1**A).

Goodarzi and colleagues investigated the combined effects of noise exposure and silver nanoparticles (Ag-NPs) on the cochlear function in rats [119]. The influence, either beneficial or detrimental, of nanoparticles, in general, on biological functions of the organism is a swiftly expanding research topic [98][120][121][122]. However, metallic nanoparticles, in particular, exploit toxic effects on cells by increasing the ROS production and pro-inflammatory cytokine release [123]. Ag-NPs can enter the body in various ways, e.g., via ingestion, inhalation or even skin contact [124]. Previous studies have reported toxic effects of Ag-NPs to the cochlea [125][126][127]. Goodarzi et al. compared completely untreated Wistar rats with rats exposed to loud noise (104 dB) for different time intervals. The animals either received not further treatment or were intra-peritoneally injected with Ag-NPs (100 mg/kg body weight). The group measured distortion product otoacoustic emissions (DPOAEs) for screening the inner ear function [128][129]. Animals showed a higher rate of hearing loss when exposed to both noise and Ag-NP at frequencies of 7.26, 8.47 and 9.86 kHz. Oppositely, malondialdehyde (MDA) and SOD levels in the serum were either increased by noise exposure or Ag-NP treatment alone but were not further increased by the combined treatment. qRT-PCR analysis further showed that *TNFSF2*, *IL6* and *NOX3* gene expressions in the cochlea were increased by one of the treatments alone but were not further increased by the combinatory treatment. Further investigations concerning Nox3-derived ROS were not made. A similar research topic was investigated by Shahtaheri et al. The group investigated the effects of white noise in combination with aluminum oxide (Al_2-O_3) nanoparticles (AO-NPs) on the cochlear structure in rats [130]. AO-NPs are widely used as thermal insulation material [131], and the exposure to workers that are involved in AO-NPs manufacturing [132][133][134] is correlated with many harmful effects on workers' health [135][136][137]. Additionally, workers are often exposed to extreme noise levels. Regarding this harmful work environment, Shahtaheri and colleagues analyzed the combinatory harmful effects of AO-NPs and noise exposure (95 dB/20 Hz–20 kHz, 8 h per day) on the cochlea of Wistar rats. The group detected reduced auditory capacities analyzed by DOPAE measurements [76][138] and cochlear damage by histochemical analysis in rats exposed to noise. The damage was further increased by treatment with AO-NPs. AO-NP treatment alone did not alter the investigated parameters. Notably, Nox3 mRNA levels also increased after noise exposure in the cochlea, while AO-NP treatment alone did not change the mRNA expression levels of Nox3. The combinatory effect of both increased Nox3 mRNA expression significantly in comparison to noise exposure alone. This was accompanied by OHC and a supporting cell decrease, while IHC numbers showed no alterations. The authors suggested an enhanced damaging effect of white noise exposure and AO-NP treatment on the cochlea due to increased Nox3-mediated oxidative distress. Critically, neither Nox3 knock-down experiments nor ROS measurements were performed in this context. Hence, again direct evidence for a Nox3 involvement is missing in this study.

1.2. Cisplatin-Induced Ototoxicity

Cisplatin is a commonly used chemotherapeutical agent against solid tumors [139][140][141][142][143]. Similar to most chemotherapeutical applications, cisplatin treatment results in strong side effects for the patients like nephrotoxicity and ototoxicity [83][144][145][146][147][148]. Cisplatin-induced nephrotoxicity can be treated with diuretics [149][150], while cisplatin-induced ototoxicity is a much more severe, cumulative and untreatable problem [18][147][151]. It manifests as sensorineural, irreversible hearing loss [152][153][154][155][156] due to damage of the organ of Corti in the cochlea [4][157][158][159]. Specifically, cell death of IHCs and OHCs [83][160][161][162], of spiral ganglion cells [163][164][165][166] and of marginal cells of the stria vascularis [167][168] is increased after cisplatin treatment. Inflammation after cisplatin treatment is another driving factor, which further progresses the cochlear damage [169][170][171][172][173][174]. On the sub-cellular level, cisplatin-mediated cytotoxicity induces DNA damage [175][176], mitochondrial dysfunction [177][178] and increased ROS production by various ROS sources [40][110][178][179][180][181][182]. The accumulating damage due to the oxidative distress further progresses the dysfunction of cochlea [28][160] and vestibular system [182][183][184].

Banfi and colleagues first reported cisplatin-induced Nox3-mediated ROS production by using a co-expression system in HEK293 cells [110]. Mukrerhajea et al. provided further evidence in vivo in the rat cochlea and in vitro in the OHC line UB-OC-1 [185]. Cisplatin treatment induced in both systems increased Nox3 expression and ROS production [186]. Kim and colleagues investigated the role of Nox enzymes during cisplatin-induced ototoxicity in general [187]. They used the mouse auditory cancer cell line HEI-OC1 and in vivo experiments for this approach. Cisplatin treatment induced Nox1 and Nox4 mRNA expression starting after 1 hour. Unfortunately, they claimed that Nox3 mRNA was not detectable; however, the data were not shown in the publication. Notably, in vivo injection of cisplatin for 4 days showed a strong induction of the already basally expressed Nox3 mRNA in the cochlea. However, the group focused on Nox1 and Nox4, and Nox3 as ROS source was not further analyzed. Mohri and colleagues investigated, besides several other important Nox3-related topics, also the role of Nox3 during cisplatin-induced hearing loss [61][188]. The group used their well-established reporter system with the dtTomato-coupled Nox3 protein [59]. Tone-burst stimuli (8, 16, 24 and 32 kHz) were applied on 2-month-old WT

and Nox3-deficient mice either treated with cisplatin or left untreated. ABR threshold shifts were measured, and WT animals showed deteriorated ABR thresholds at frequencies of 24 and 32 kHz after cisplatin treatment compared to Nox3-deficient animals, which showed no deterioration. WT mice also showed OHC loss, which was lower in Nox3-deficient mice. TdT-mediated dUTP-biotin nick end labeling (TUNEL) assays confirmed increased apoptosis of OHC in WT animals in this context as reported before [61][189]. In Nox3-deficient animals fewer TUNEL-positive OHC were detected. In the lateral wall of the cochlea and the stria vascularis no TUNEL-positive cells were seen in both WT and Nox3-deficient mice. The group furthermore showed that cisplatin treatment increased Nox3 expression in the cochlea predominantly at the basal turn and in the supporting cells. In detail, no Nox3-expressing OHC either with or without cisplatin treatment could be detected in WT animals, while weak Nox3-expression in IHCs and strong Nox3 expression in supporting cells could be observed at least after cisplatin treatment. Together, these studies provide solid evidence that cisplatin treatment increases the presence of Nox3 in the cochlea, which leads to a harmful elevation of ROS production and finally to ototoxicity. Interestingly, in vivo Nox3 is mainly present in the supporting cells and not the OHCs, which nevertheless suffer the greatest damage through the increased ROS production (**Figure 1**A).

Several studies have provided evidence for a protective role of the activating adenosine A1 receptors (A1ARs) [190] and its agonist adenosine during cochlea-related diseases [113][191][192][193][194][195][196][197][198]. In this context, Kaur and colleagues investigated the role of ROS for the A1AR signaling during cisplatin-induced ototoxicity [115]. They reported that activation of the A1AR signaling pathway by N6-R-phenylisopropyladenosine (R-PIA) prevents hearing loss induced by cisplatin and OHC damage in the rat in vivo. They used the OHC line UB-OC-1 to investigate a role for Nox3-derived ROS in vitro, since ROS have a pro-inflammatory effect during cisplatin-induced ototoxicity [110][186]. Cisplatin treatment for 24 h induced A1AR mRNA and protein expression and increased Nox3 mRNA as well as the total cellular ROS levels. Treatment with R-PIA reduced ROS generation and Nox3 mRNA expression in UB-OC1 cells and in the rat cochlea. Cisplatin treatment of UB-OC-1 cells also induced phosphorylation and nuclear translocation of Signal transducer and activator of transcription 1 (STAT1), which could be inhibited by additional R-PIA treatment. STAT1 signaling contributes to the pro-inflammatory response during cisplatin-induced ototoxicity [199]. Accordingly, treatment with R-PIA reduced cisplatin-induced expression of TNF in the rat cochlea. However, no experiments after Nox3 knock-down or knock-out were performed. Therefore, evidence for the identification of Nox3 as relevant ROS source in this context is missing.

1.3. Cytomegalovirus-Induced Hearing Loss

Congenital Cytomegalovirus (CMV) infection often leads to sensorineural hearing loss accompanied by neurological and developmental disabilities [200][201][202][203]. Several studies have monitored apoptotic cell death in the murine cochlea [204] in neonatal mice after CMV infection, subsequently leading to sensorineural hearing loss [205][206]. A correlative increase in total cellular ROS levels was also described in this setting [205]. Due to these previous observations, Zhuang and colleagues picked this topic up and investigated the possible ROS sources and the effect of the anti-inflammatory substance Berberine [207] during CMV-induced ototoxicity [208]. The group detected an increase in apoptosis and total cellular ROS in neonatal murine ex vivo cultured spiral ganglion cells. An increase in Nox3 protein expression was also observed. Additional treatment of Berberine reduced apoptosis, ROS levels and Nox3 expression. However, no genetic evidence was given to validate Nox3 as ROS source. Most critically, the authors claimed that Nox3 was connected to mitochondrial ROS production. No specific mitochondrial ROS measurements were performed, and no co-localization studies of Nox3 with mitochondria, e.g., by immunolabeling and fluorescence microscopy, were conducted. Nevertheless, this is so far the one and only study that has described an induction of Nox3 protein expression as response to infection.

1.4. Age-Induced Hearing Loss

Age-induced hearing loss (presbycusis) [209] affects, as the name implies, elderly people. This disease is associated with tremendous social consequences [210][211][212][213]. Similar to other causes for hearing loss, age-induced hearing loss can further progress due to prolonged noise exposure or ototoxic drugs [214]. On the cellular level, the loss of hair cells, spiral ganglion cells and cells of the stria vascularis leads to hearing loss majorly at higher frequencies [211][215]. An increase of age is also accompanied with a disturbance of redox homeostasis not only in the cochlea [22][34], but also in other organs, since gene expression of anti-oxidant systems decrease with age [23][35][36].

Du and colleagues investigated the effects of a HFD in combination with a D-galactosidase-induced rat animal model of aging [216][217] to investigate the cumulative effects on hearing loss [218]. In this animal model, the continuous administration of D-galactose leads to numerous detrimental effects based on metabolic disturbance that mimic the aging process [216][219][220][221]. These effects include dysfunctional mitochondria [220][222][223], increased apoptosis [224][225], neurotoxicity [220][226][227], a shortened lifespan [228] and, after 8 weeks of treatment, symptoms that mimic aging of the cochlea due to increased ROS production [229][230][231][232]. Furthermore, after 8 weeks of D-galactose treatment deletions

in the mitochondrial DNA (mtDNA) in the cochlea increase and mitochondria show an oval round shape indicating massive damage. The isolated mtDNA from rat cochlea cells showed increased oxidative damage and subsequent common deletion, which are both biomarkers for oxidative distress, aging and age-related hearing loss [216][233][234][235][236][237]. Du et al. analyzed ABR thresholds and detected the highest ABR threshold shifts for four tested frequencies (4, 8, 16, 32 kHz) in groups treated with both HFD and D-galactose after 12 months. After sole D-galactose treatment Nox3 protein levels increased in the stria vascularis and the spiral ganglion. HFD treatment alone increased Nox3 protein levels only in the stria vascularis. The combined treatment of D-galactose and HFD led to the highest Nox3 expression not only in the stria vascularis and the spiral ganglion, but also in the organ of Corti. Apoptotic cell death in the inner ear was observed for all three conditions, but again the highest cell death rate was reported after the combined treatments. Additionally, all three treatments increased the accumulation of mitochondrial common deletion [238][239], which accompanies mitochondrial damage due to aging [240][241]. Du and colleagues deepened their findings from this previous study [218] with the same D-galactose-induced aging model via RT-PCR and Western blot analysis and reported an increase in Nox3 and p22^{phox} mRNA and protein expression in D-galactose-treated rats in the cochlea [112]. Additional Western blot analysis and TUNEL staining showed that apoptosis increased in the cochlea after D-galactose treatment. These two studies by Du and colleagues gave the first correlative insights of increased Nox3 expression during aging, an associated damaging effect to cochlear structures and the subsequent hearing loss. However, since mitochondria are heavily damaged during this aging model and neither in vivo experiments with Nox3-deficient animals nor in vitro experiments with Nox3 knock-down in cells were conducted, the explicit role and the contribution of Nox3-derived ROS in comparison to ROS produced by the damaged mitochondria remained elusive.

Rousset and colleagues used the A/J mouse strain nmf333, which carries a missense mutation in the p22^{phox} subunit [242], to characterize the role of Nox enzymes in the cochlea during age-induced hearing loss [8]. The group firstly defined age-induced hearing loss in WT animals in their experimental setting. They analyzed ABR threshold levels over an age range from 4 to 26 weeks and observed threshold shifts close to 45 dB after 4 weeks, which progressed up to 75 dB with age. They also detected a progressive hearing loss 32 kHz (in 4-week-old mice) and 5.7 kHz (in 26-week-old mice). In accordance with these data sets, a progressive degeneration of the sensory epithelium from the base to the apical turn was described with a more pronounced cellular degeneration in the basal region. Further analysis of IHC innervation revealed a dramatic decrease in the number of synaptic ribbons per IHC, as well as a decrease in the total neuronal density in the spiral ganglion, which also progressed with age. Since a deficiency of p22^{phox} affects Nox1-4, the group analyzed the presence and distribution of Nox mRNA expression in both the mouse and, highly notably, in the human cochlea. qRT-PCR and in RNAscope in situ hybridization measurements showed high mRNA expression of Nox2, Nox3 and Nox4 in mouse and human cochlea tissue. While Nox2 and Nox4 mRNA was evenly distributed throughout the whole cochlea, Nox3 mRNA was concentrated in the spiral ganglion and moderately expressed in the stria vascularis. Most interestingly, Nox3 mRNA was not detected in hair cells, which is in line with the study from Mohri et al. [59]. p22^{phox}-deficient animals showed no disturbance in hearing at young age in comparison to WT mice. However, the loss of the hearing capacities at high frequencies observed in aged WT mice, was nearly absent in p22^{phox}-deficient animals together with an intact sensory epithelium and preserved synaptic ribbons. The group further performed a transcriptome analysis of 6-week-old cochlea tissue and detected a down-regulation of ryanodine receptors (Ryr) 1, 2 and 3, which are important for Ca^{2+} homeostasis and accordingly for proper neuronal signaling. Several other genes, all revolving around Ca^{2+} homoeostasis, such as *Otoferlin*, *Vamp1*, and *Snap25* or the glutamate transport, such as *Slc17a6*, *Slc17a8* and *Gria2* were down-regulated in absence of p22^{phox}. The group narrowed down the auditory neurons as main cell type where the down-regulation was observed. This remarkable study firstly analyzed the mRNA expression of Nox3 in the human cochlea and clearly solidified a rather detrimental effect of Nox presence on cochlear structures, precisely the neuronal part. Unfortunately, like in other previous studies of the Nox3 research field, the group did not clarify the exact interplay of Nox-derived ROS during Ca^{2+} signaling and the subsequent age-related hearing loss. Moreover, while nicely showing that also Nox2 and Nox4 mRNA is present in the cochlea, the analysis of p22^{phox}-deficient animals only enabled suggestions considering the general role of Nox enzymes in the cochlea and not specifically the role of Nox3, especially since Nox2 and Nox4 might also play important roles in this organ [243][244][245]. Protein expression, for example, in cochlea tissue lysates, was not analyzed, Instead, the research group solely relied on mRNA-detecting techniques. Since the opinion that mRNA always correlates with protein presence or even activity of the protein is outdated [246][247][248][249][250], protein level analysis of the cochlea, especially from human samples would have been a ground-breaking contribution to the field of Nox3-related research. Human-related data sets of this topic are still largely missing to date. In their favor, the group mentioned and discussed these critical points already in their paper. In summary, the studies of Rousset and colleagues [19][62][251], together with Mohri et al. [59] represent milestone research articles considering Nox3 investigations in the inner ear. Continuing in this sense, Mohri and colleagues also investigated the topic of age-induced hearing loss with their generated mouse line, which expresses the fluorescent reporter dtTomato in cells that display Nox3 expression [59]. The group compared the ABR threshold shifts in WT and Nox3-deficient animals after 1, 2 and 6 months after birth. An

increase of Nox3 protein in the cochlea as well as increased ABR threshold shifts at frequencies of 8, 24, and 32 kHz occurred in WT mice over time. Nox3-deficient mice showed no ABR threshold shift increase at all. Especially at high frequencies (24 and 32 kHz), the ABR thresholds were higher in WT mice in comparison to Nox3-deficient animals at 6 months from birth. In addition, histologic analysis of the organ of Corti showed that WT mice at 6 months after birth exhibited OHC loss, while hair cell loss in Nox3-deficient mice was significantly lower. These findings suggest that increased Nox3 expression in the organ of Cori leads to OHC destruction and subsequently contributes to age-related hearing loss (**Figure 1**A).

2. Role of Nox3 during Vertigo

The only study which investigated a rather harmful effect of Nox3-derived ROS on the vestibular system (in contrast to the crucial function of otoconia formation), was conducted by Zhang et al., who investigated factors that influence benign paroxysmal positional vertigo (BPPV) [252]. BPPV is the most common peripheral vertigo-related disease [253][254] occurring in 2.4% of people [255], which increases with age [256]. BPPV is characterized by the detachment of otolith particles, particle movement into the semicircular canal and subsequent loss of otoconial function [257][258]. BPPV is therefore also termed otolithiasis. In dependency how the proper function of the otoconia is impaired, BPPV can be classified in primary BBPV and secondary BPPV. Primary BBPV is induced by factors that directly damage the otoliths or their surroundings, e.g. hair cell damage or loss, endolymph ion changes, decreased otolith protein secretion and defects in otolith-anchoring proteins [257][259]. Secondary BBPV is defined as damage, which is induced as side effect of other harmful events, such as ear surgery, trauma, ototoxic drugs, Meniere's disease [260] or vestibular neuronitis [261]. Systemic factors like osteoporosis [262], vitamin D deficiency, hypertension, diabetes or cerebrovascular diseases [263] can also contribute to the severity of this disease. Zhang and colleagues focused on vitamin D deficiency during BPPV, since vitamin D is important for proper Ca^{2+} homoeostasis in general [264][265] and for proper otolith formation and function in particular [261]. Overall, 48 patients with diagnosed BPPV and 48 control patients from the Affiliated Hospital of Inner Mongolia Medical University [266] were analyzed in this study. While no difference in age, body mass index, sex, occurrence of diabetes or hypertension was observed between the groups, BBPV-diagnosed patients showed a decreased bone density and plasma vitamin D levels. Notably, mRNA and protein levels of both OC-90 and Nox3 in the serum were decreased in patients with BPPV. To further analyze the role of vitamin D in this context, vitamin D receptor (VDR)-deficient mice were analyzed. In whole-tissue lysates of the inner ear, mRNA and protein levels of OC-90 and Nox3 were decreased in VDR-deficient mice suggesting a regulatory role of vitamin D in this context. A direct mechanism for VDR-mediated signaling for Nox3-derived ROS production and OC-90 assembly was not investigated.

3. Role of Nox3 during Lung Diseases

For a long time, Nox3-related research only focused on either the inner ear or studies focused on broad expression studies to improve the catalogue, which lists if, when and where Nox isoforms are expressed. Most of the latter studies have not focused explicitly on Nox3, but rather described its expression as additional finding. Zhang and colleagues investigated, for the first time, a possible connection between Nox3 and pulmonary emphysema, which is a major contributor to chronic pulmonary diseases [267][268] in a mouse model [64]. They described developing emphysemas in naive TLR4- and MyD88-deficient mice beginning at 3 months after birth and peaking between 6 months and 1 year. This was reflected by increased lung volumes, enlarged air spaces distal to the terminal bronchioles and by destruction of the normal alveolar architecture. These factors are typical for emphysema [267] and occurred in both knock-out animal strains. Notably, all mice strains did not show any significant differences in any pro-inflammatory parameter that was analyzed. However, TLR4-deficient animals showed a decreased elastase inhibitory capacity and increased elastolytic activity in the lung tissue. Since increased oxidative distress is an important correlative factor of emphysema [269] and lung injuries [270][271][272][273][274][275][276][277], the group analyzed the total antioxidant capacity, namely levels of glutathione (GSH) and other antioxidant components in the branchio-alveolar fluid. A strong decrease of GSH levels was detected in the fluid of knock-out animals. Moreover, isolated lungs and isolated lung cells from TLR4-deficient animals showed increased O_2^- production in comparison to WT animals. The increased ROS levels further led to more oxidative DNA damage, which is also correlated with emphysema [278]. Interestingly, while Nox3 mRNA was only weakly expressed in WT animal lungs and isolated endothelial lung cells, TLR4-deficient lung samples and lung cells showed an increased Nox3 mRNA expression. Additionally, isolated lung cells from TLR4-deficient animals showed an increased elastolytic activity similar to the lung tissue. Knock-down of Nox3 via siRNA in TLR4-deficient lung cells led to a rescue effect of elastolytic activity, nicely confirming the involvement of Nox3. These results clearly demonstrated the connection of TLR4 deficiency, increased Nox3 expression, Nox3 as cause for the increased elastolytic activity and therefore the developed emphysema. A direct mechanism for Nox3-derived ROS was not investigated at that time. Nevertheless, the study of Zhang and colleagues broke the "inner ear" stigma of Nox3 in terms of disease developement.

In a follow-up study from Zhang and colleagues, a role of Nox enzymes during hyperoxia was investigated. Hyperoxia can occur during sustained oxygen supply in critically ill patients, which can result in respiratory failure [279][280]. Hyperoxia is also an established model for oxidant-induced lung injury [281][282]. Previous reports of the group demonstrated that TLR4-deficient mice showed increased oxidant production in lung tissue and subsequent lung destruction [64], as well as enhanced susceptibility to hyperoxia-induced acute lung injury [283]. An increase in Nox3 mRNA was also reported in TLR4-deficient animals, and siRNA-mediated knock-down partially rescued the phenotype related to TLR4-deficiency [64]. WT mice exposed to hyperoxia showed increased TLR4 mRNA and protein levels in mouse lung endothelial cells and lung lysates. TLR4-deficient mice were more susceptible to hyperoxia, as reported before [283], but interestingly, Nox3-deficient animals showed an increased survival rate. Additional knock-out of Nox3 in TLR4-deficient animals (TLR4/Nox3 double-deficient mice) nearly rescued the animals comparable to WT controls. Hyperoxia conditions increased macrophage, lymphocyte and neutrophil infiltration into the lungs of WT animals, which was further enhanced in TLR4-deficient animals. Nox3-deficient animals, however, showed no differences compared to WT animals. Notably, TLR4/Nox3 double-deficient animals showed a partial rescue from this phenotype. In WT mice, increased lactate dehydrogenase release as well as increased H_2O_2 and lipid peroxidation levels were detected in lungs after hyperoxia exposure. TLR4 deficiency further increased these parameters, while Nox3-defcient animals showed reduced levels in comparison to WT animals. These data nicely show that TLR4 signaling somehow inhibits Nox3-mediated ROS production in lungs, which is uncoupled when TLR4 as regulating factor is missing. The Nox3-mediated uncontrolled ROS production then leads to lung destruction. When Nox3, as an ROS source, is removed, it either protects the mice in general from lung injury during hyperoxia, or it leaves the TLR4-dependent inhibition as the terminal factor without any effect. The group also discovered that the Heat Shock Protein 70 (Hsp70) [284][285] is necessary for the TLR4-mediated Nox3 inhibition, since mice and endothelial lung cells deficient for Hsp70 showed increased Nox3 mRNA and protein levels. Notably, mitochondrial matrix O_2^- levels were decreased in TLR4-deficient lung cells and were not altered in Nox3-deficient cells, excluding mitochondria as a potential ROS source in this setting. In addition, this study firstly investigated possible transcription factors that might influence Nox3 mRNA expression. Chromatin immune-precipitation assays identified regions between −2534/−2360 and −1792/−1498 base pairs upstream of the Nox3 promoter as critical binding sites for STAT3 during Nox3 inhibition. In lungs and endothelial lung cells from endothelial STAT3-deficient mice, more Nox3 expression during both basal and hyperoxia conditions was detected. Electrophoretic Mobility Shift Assay (EMSA) analysis showed that Hsp70 induced the STAT3 binding to the Nox3 promoter region only in WT or Myd88-deficient endothelial lung cells, but not in TLR4- or TRIF-deficient cells. Taken together, this study by Zhang and colleagues is probably the most detailed report about Nox3 activation, regulation and function in a specific context so far. The results were solidified by genetic models and ROS measurements not only in vitro, but also in vivo and no cell type or tissue switching during the study was performed. This is a remarkable example of how to perform a scientific analysis about a Nox enzyme and its functions (**Figure 1**A,B).

Ruwanpura and colleagues further investigated the role of TLR4 and its adaptors MyD88 adapter-like/Toll/interleukin-1 receptor domain-containing adaptor protein (MAL/TIRAP) [286][287] for normal lung architecture and function in mice [288]. They confirmed the findings from Zhang and colleagues [64], i.e., enlargement of the distal air spaces and destruction of normal alveolar architecture without any inflammation in 6-month-old TLR4-deficient mice. Functionally, they found that the static compliance (pulmonary compliance during the inspiratory pause) was significantly increased in TLR4-deficient mice, which was determined by forced oscillatory technique [289][290][291]. The group further described increased oxidative distress in lung tissue, increased Nox3 mRNA and increased apoptosis of alveolar septal cells. Notably, TLR2 deficiency did not alter any of the observed parameters suggesting a TLR4-specific mechanism in this context.

Yasuoka et al. focused on the influence of ROS during the development of lung fibrosis [292]. During lung diseases, fibrosis is a common side effect, which poses a significant increase in morbidity and mortality in patients [293][294][295]. ROS have been implicated as drivers of fibrosis-related pathophysiology [296][297][298] and lung dysfunction [299][300][301]. Fibrosis is accompanied with tissue remodeling and tissue growth as well as development and is regulated by a plethora of growth factors. Yasukoa et al. focused on the insulin-like growth factor binding protein-5 (IGFBP-5), a prominent factor in this context [302][303], and its connection to lung fibrosis and ROS production. They found that primary human lung fibroblasts increased Nox3 mRNA levels and total cellular ROS production after IGFBP-5 or TGF-β treatment. siRNA-mediated knock-down of Nox3 reduced the ROS production in these cells to baseline levels. However, a role for Nox3-derived ROS in the investigated in vivo setting was not conducted.

The discovery of Nox3 as important player for the progression of lung diseases was furthermore confirmed by a series of genetic screens, which delivered correlative data between the *NOX3* gene and different lung diseases. Tremblay et al. conducted a GWAS to identify candidate genes as predisposing factors for genetic asthma association studies [304]. The scan, in combination with the Genes-to-Diseases computational analysis tool [305][306], analyzed 609 subjects from the Saguenay-Lac-St-Jean founder population in Quebec, Canada [307][308]. Amongst several other genes, the *NOX3* gene

was identified as the only NADPH oxidase-related gene. Yin et al. investigated genetic etiology in the context of non-idiopathic pulmonary hypertension (PH) [309][310][311]. Overall, 208 patients were included, 109 patients were diagnosed with non-idiopathic PH and 99 healthy volunteers were included as controls. A total of 143 SNPs were detected in the 109 PH patients with the top hits located in the chromosome 6, precisely in the locus of the *NOX3* gene (SNP termed rs6557421). Notably, PH patients with the detected SNP rs6557421 genotype had a 10-fold-higher risk to develop PH in comparison to healthy control samples. Cantu et al. searched for genetic variations that might increase the risk of primary graft dysfunction (PGD) after lung transplantation by a SNP set analysis [312][313]. Rejection of the grafted lung and subsequent organ dysfunction is a major cause of death during the early transplantational period, affecting up to 30% of all patients [314][315][316]. One of the major pathophysiological aspects associated with PGD is increased oxidative distress occurring during ischemia/reperfusion events [317][318][319][320]. In total, 1039 lung transplant recipients and 392 donors were included in this study, and 314 of the 1038 recipients developed PDG and four genes were identified encoding glutathione peroxidase 1 (*GPX1*), nuclear factor (erythroid-derived 2)-like 2 (*NFE2L2*), nitric oxide synthase 3 (*NOS3*) and glutathione S-transferase mu 2 (*GSTM2*), which all are involved in antioxidant responses [321][322][323]. In the donor group, the genes for Nox3 (*NOX3*), nitric oxide synthase 1 adaptor protein (*NOS1AP*) and paraoxonase 1 (*PON1*) were associated with the development of PGD. Within the *NOX3* gene, the SNP rs3749930 had the strongest association with PGD. The detected SNP marks a nucleotide conversion, which resulted in a threonine to lysine aa substitution in a trans-membrane portion of the Nox3 protein. In addition, several intronic SNPs within the *NOX3* gene were associated with increased risk of PGD.

All of these studies clearly demonstrate a critical involvement for Nox3-mediated ROS production as rather destructive factor during lung diseases.

4. Role of Nox3 during Cardiovasclar Diseases

The term "cardiovascular diseases" summarizes a broad catalogue of diseases that affect one or many components of the cardiovascular system directly. This includes the heart or the blood circulation system, but also simply all other organs and parts of the body as well, since oxygen and nutrient supply, mediated by the blood stream, are crucial for proper functioning of the organism. Thus, this topic intervenes with many other diseases, which are affected by the cardiovascular system. Similar to nearly any other disease outcome, as well as during any kind of cardiovascular disease, increased ROS production is a major contributing factor that worsens diseases progression [324][325][326][327][328][329]. Of course, the involvement of Nox enzymes as ROS sources was intensively investigated, including Nox3 [330].

4.1. Nox3 and Type 2 Diabetes

While fatty acids are crucial components of cellular membranes, chronically increased levels of FFA, consumed with a HFD lead to obesity due to excessive depositing in non-adipose tissues, e.g. the liver [331][332][333][334]. Subsequently, the development of insulin resistance [335][336], type 2 diabetes [337] and other hepatic diseases [338] dramatically increases. *Diabetes mellitus* affects more than 300 million people worldwide and represents a disease with high morbidity [339][340]. Type 2 diabetes is associated with various chronic and acute toxic side effects, leading to dyslipidemia, hyperglycemia [341][342][343], diabetic retinopathy [344][345] and chronic hyperinsulinemia. All of these conditions can further induce or enhance adipositas, which is closely related to insulin resistance [346][347][348][349]. Type 2 diabetes and insulin resistance often correlate with increased oxidative distress and an increased systemic pro-inflammatory profile [350] in the according tissues and cells, especially in the liver. Of course, the roles of the Nox isoforms, as primary ROS producers, were investigated in this context [330]. Since Nox3 was identified as an important ROS source in association with diabetic diseases in vitro for HepG2 cells [351][352] (Section 5.1.4) and in a mouse model in vivo [335], further research mostly focused on treatment options. Cremonini et al. investigated the role of the flavanol (-)-Epicatechin [353][354] during HFD-induced insulin-resistance in mice [355]. The group detected a strong up-regulation of Nox3 (60%), Nox4 (274%) and p22^{phox} (237%) protein levels in the liver of mice, which received a HFD in comparison to normally fed mice. Supplemental Epicatechin in the diet prevented this up-regulation. On the in vitro level, similar results were observed in HepG2 cells treated with palmitate and Epicatechin, with exception of p22^{phox}, which remained unaltered. The increased expression of Nox3 and Nox4 resulted in an increased total cellular ROS production. No genetic evidence was provided, and only inhibitors for Nox enzymes were used. Therefore, the specific role of Nox3 or Nox4 could not be determined.

Gupta et al. investigated the effects of Pancreastatin (PST) on adipocyte cells in vitro and in vivo [356]. PST is a peptide secreted by neuroendocrine cells [357], which exploits diabetogenic effects, such as glucose uptake inhibition in liver cells [358][359] or the pancreatic β cell response to insulin [360][361]. Accordingly, treatment with PST is associated with insulin resistance, type 2 diabetes and adipositas [362][363][364]. Since increased ROS levels are involved in lipolysis of adipocytes [246][365] and often correlate with type 2 diabetes progression in patients [330][366][367], the effects of PST on the oxidative

distress and chronic insulin induced lipogenesis were also investigated in this study. Neither insulin treatment nor PST treatment alone were sufficient for induction of total cellular ROS production in the adipocyte-like cancer cell line 3T3-L1. Combined treatment induced a slight increase of ROS levels. This corresponded with increased Nox3 protein expression and JNK1/2 phosphorylation. An increase of Nox3 protein expression and JNK1/2 phosphorylation was also detected in white adipose tissue of mice with artificially induced insulin-resistance [368]. While these results nicely contributed to previous findings [335][351][352], no siRNA-mediated knock-down of Nox3 or Nox3-deficient animals were used to clearly confirm Nox3 as the responsible ROS source. Building up from their previous study, the group around Gupta and colleagues researched on possible treatment options with the Pancreastatin inhibitor PSTi8 against insulin resistance [369]. Palmitate treatment of HepG2 cells resulted in lipid accumulation, increased Nox3 mRNA expression, total cellular ROS production and decreased glycogen synthesis. All of these effects were reversed by additional treatment of PSTi. PA also induced phosphorylation of JNK1/2 and p38, which was again prevented by PSTi8 treatment. These findings mark PSTi8 as a potential candidate for diabetic treatment. However, since in both studies, Nox3 was not confirmed as a responsible ROS source, especially since Nox4 is also a prominent ROS source in adipocytes [370][371][372], a clear involvement for Nox3-derived ROS remains elusive.

Malik et al. investigated a previously described therapeutic role of Pterostilbene against insulin resistance [373]. Several studies already described anti-cancer and anti-oxidant effects of Pterostilbene [374], which is a methoxylated Reservatrol analogue [375]. An anti-diabetic effect was also described [376][377][378]. A mechanism of action was not investigated yet. Malik et al. treated HepG2 cells with palmitate, which induced cell death, lipid accumulation, Nox3 mRNA expression, total cellular ROS production and lipid oxidation. Additionally, PA treatment increased expression of genes for proteins involved in fatty acid metabolism, i.e., Sterol regulatory element–binding protein (SREBP1c), Carnitine palmitoyl transferase1 (CPT1), a mitochondrial PA transporter and its transcription factor Peroxisome proliferator-activated receptor alpha (PPARα). All of these effects were strongly reduced after additional treatment with Pterostilbene. While anti-oxidant effects were previously described for Pterostilbene, contradictory, the group observed down-regulation of anti-oxidative enzymes after additional Pterostilbene treatment, therefore outruling an anti-oxidative effect in this context. Since no siRNA knock-down of Nox3 was performed a direct effect of Pterostilbene on Nox3-derived ROS production was not investigated.

Type 2 diabetes negatively affects the outcome of wound healing [379][380] and increased ROS levels correlate with chronic open wounds in patients suffering from *Diabetes mellitus* [381]. Kim et al. investigated a possible treatment option for improved wound healing [382] by testing the anti-oxidative substance Edaravone. Edaravone was already in use for treatment of acute cerebrovascular diseases [383]. The group used primary human dermal fibroblasts from patients or healthy controls and used the human keratinocyte cell line HaCaT. Furthermore, they conducted a murine in vivo wound healing experiment [384]. Using this model, the group could analyze the expression of Nox3 in tissue flaps near the wound healing area and observed no differences between normo- and hyperglycemic mice after 5 days of operative wound creation. The addition of fibrin for wound healing stimulation or the application of Edaravone did not change Nox3 protein expression. Since no ROS measurements with siRNA knock-down of Nox3 or Nox3 deficient cells were performed, the role of Nox3-derived ROS during the wound healing process remains elusive.

As in the case of lung diseases [304][309][312], also for cardiovascular diseases, GWAS studies were conducted to identify possible risk factors which might influence the disease outcome [385][386][387]. Radowski et al. performed a GWAS to identify genes related to hypertension in 340 patients with type 2 diabetes [388]. Among the six identified genes, the *NOX3* gene was also detected, which was previously associated with hypertension [389]. Kwak et al. conducted a GWAS of people with type 2 diabetes to broaden the spectrum of factors, which could help identifying risk factors for cardiovascular diseases in general and type 2 diabetes in particular before the disease outbreak occurs [390]. In their pre-print, they described three variants in genetic loci associated with cardiovascular diseases, especially with type 2 diabetes. Among them, on chromosome 6, there was an intergenic variant between the genes *TFB1N* and *NOX3* (SNP termed rs335407).

4.2. Nox3 and Adipositas

Similar to type 2 diabetes and insulin resistance, ROS also play a role during the inflammatory settings associated with adipositas [346][391][392][393][394]. In adipocytes, the presence of Nox3 was reported before [356]. Issa et al. investigated the influence of cytokines on ROS production and lipolysis in the adipocyte-like cell line 3T3-L1 [246]. Treatment with various pro-inflammatory cytokines (TNF, IL-1β, IFN-γ) induced a slight increase in cellular O_2^- production after 8 h in differentiated 3T3-L1 cells. It was previously shown that Nox4-derived ROS play an important role for adipocyte differentiation [370][371][372]. Undifferentiated and differentiated 3T3-L1 cells expressed Nox3 as well as Nox4 mRNA. However, only differentiated cells contained the produced Nox3 and Nox4 proteins. While Nox4 expression remained unaltered after cytokine treatment, Nox3 protein levels strongly increased after 8 h. This study nicely showed a decrease in ROS production via Nox3-knockdown after cytokine treatment. Nox-derived ROS were associated with lipolysis in

adipocytes before [365] and, indeed, Nox3 knock-down led to an increased lipolysis in 3T3-L1 cells. On the mechanistic level, the group identified an increased phosphorylation of the hormone-sensitive lipase, an enzyme which mediates lipolysis in adipocytes, at the serine residue 536.

4.3. Nox3 and Stroke

Stroke is a major consequence of hypertension [395][396], and elevated ROS levels have been associated with cerebral hemorrhage [397][398][399]. Michihara and colleagues therefore investigated the role of Nox enzymes during stroke development [400]. The group analyzed the cerebrum in a spontaneously hypertensive rat (stroke-prone) model (SHRSP) [401]. These SHRSP animals show lower serum cholesterol levels [402] and increased levels of oxidized proteins in the aorta, heart, kidney [403] and brain [404]. Furthermore, increased 8-OHdG levels in the urine and increased ROS levels in the brain of 16-week-old SHRSP animals were reported [405]. Increased O_2^- levels, enhanced general Nox activity and increased SOD protein levels were also detected in the brains of SHRSP animals [406]. Michihara et al. analyzed the mRNA levels of Nox enzymes in the cerebrum of SHRSP animals and found increased mRNA levels of Nox2 and Nox3, while Nox1 and Nox4 were not altered and Nox5 was not detected. Notably, Nox3 protein levels were also increased, while Nox2 levels did not change in comparison to the control animals. This is a nice example that both mRNA and protein levels should always be investigated when suggesting changes in protein presence. However, again, no siRNA-mediated knock-down or Nox3 knock-out model was used to provide evidence that Nox3 is the responsible ROS source for the observed effects in SHRSP animals.

4.4. Nox3 and Heart Failure

Several studies have investigated Nox enzymes and their roles for the cardiovascular system in general [407][408][409] and during human [410][411][412][413], mouse [414][415][416][417] and rat heart failure in particular [418][419]. While Nox1, Nox2, Nox4 and Nox5 were detected and investigated in this context, the role of Nox3 remained elusive until its detection in murine embryonic stem cell-derived cardiomyocytes by Li and colleagues [414]. The group mainly detected Nox4 mRNA expression, while Nox3 was only weakly expressed and accordingly focused on Nox4. Bkaily and colleagues further analyzed the role of Nox3 in this setting [420]. For this purpose, they used the hereditary cardiomyopathy hamster model [421][422][423], which is well established for cardiovascular disease studies [424]. They detected Nox1, Nox2 and Nox4, but no Nox3 protein in the ventricular heart muscles of normal hamsters. In the ventricular heart muscles of cardiomyopathic hamsters, they observed a reduction of Nox1 and Nox4 protein levels and an increase of Nox3 protein, while Nox2 levels remained unchanged. These findings nicely demonstrate that Nox isoforms can show a dynamic expression in dependency of the tissue status. The fluctuation of Nox enzyme expression also demonstrates again that siRNA-mediated knock-down or knock-out experiments are strictly needed when claiming a specific role for a certain Nox enzyme as ROS source. Unfortunately, this was also not conducted in this study.

ROS production is also associated with the pathogenesis of ischemia/reperfusion (I/R)-induced heart injuries [425][426] occurring during a myocardial infarction. These injuries include myocardial cell damage and death, arrhythmias or microvascular dysfunction [427][428][429]. Morimoto et al. investigated a putative interplay of ROS and the chemokine monocyte chemoattractant protein-1 (MCP-1) [430][431][432] during I/R [433]. In vitro experiments with neonatal cardiomyocytes showed that under normoxic conditions MCP-1 had no protective effect. However, after I/R induction, apoptotic cell death increased after 6 h and was reduced by treatment with MCP-1. They used Langendorff-perfused mouse hearts from MHC/MCP-1 mice, which overexpress MCP-1 in the heart for further in vivo investigations [434]. The group reported an increase of MCP-1 mRNA and ROS production in WT mice after I/R, which was abolished in hearts from MHC/MCP-1 mice. Notably, the group observed mRNA expression of Nox1, Nox2 and Nox3 in the hearts of WT mice, which decreased after I/R. In the hearts of MHC/MCP-1 mice mRNA levels were lower at basal conditions and rose after I/R, again suggesting a dynamic interplay of Nox-derived ROS production. Unfortunately, no Nox silencing or knock-out neither in vitro nor in vivo was performed. Furthermore, no protein expression was analyzed for Nox3. Hence, if and how Nox3-derived ROS production is activated and if these ROS are involved in the context of MCP-1-mediated cardioprotection could not be clarified.

Vats et al. performed a retrospective cohort study [435] from a population-based Malmö Diet and Cancer Study [436] with 30,446 subjects over 24.3 years. The group analyzed SNPs to detect genetic variations in genes related to oxidative distress and vitamin intake. The study focused on abdominal aortic aneurysm (AAA) [437] and unpredictable ruptured AAA [438][439], both manifesting in an irreversible and life-threatening dilation of the abdominal aorta [437][440][441]. Accordingly, the study only included participants with occurrence of AAA (25,252 patients in total) [436]. Oxidative distress has been suggested as a possible link between various factors that contribute to AAA, such as chronic inflammation and cell death [442][443], with Nox enzymes as correlated endogenous ROS sources [442][444]. During this study, 399 (1.6%) participants

were diagnosed with AAA, and 71 (0.2%) were diagnosed with rAAA in general. Furthermore, an amazing effort was made in terms of sub-analytic parameter analysis such as sex, smoking status and physical activity by integrating patient information [445]. The genetic loci were identified by GWAS and altered SNPs for the *NOX5* gene (rs150003957), and the *NOX3* gene (rs3749930) were detected. The according male patients showed elevated hazard ratios for AAA, while female patients showed no alterations. Furthermore, participants with the dominant *NOX3* gene SNP rs3749930 showed an increased risk for rAAA in the overall study. The group additionally performed subgroup analysis to investigate if the detected oxidative distress-related genotypes had an influence on the effect of antioxidant vitamin intake. They reported that men with the *NOX3* gene variant rs3749930 showed an inverse association between higher riboflavin vitamin uptake and a hazard risk for intact AAA, which was also confirmed for the overall study population after sex covariate adjusting.

5. Role of Nox3 during Renal Diseases

Chen et al. conducted a GWAS for three phenotypes associated with risk of nephropathy, i.e., serum creatinine levels, creatinine clearance and the glomerular infiltration rate [446][447][448] in 691 type 2 diabetes patients from West Africa to analyze potential factors for reduced renal functions as major consequence of diabetic diseases [389]. The screen detected linkage regions that contain genes, which might influence these three phenotypes. The most prominent candidate genes in these regions that have been implicated in diabetes-induced nephropathy and renal damage were the genes encoding p22^{phox}, (linker region 16q24), Nox1 (linker region 10q22) and Nox3 (linker region 6q25.1–6q26). Together with the study from Ye et al. [449], only two studies investigated Nox3 during kidney-related diseases.

6. Role of Nox3 during Gastrointetinal Disaeses

The most dominant Nox isoform in the gastrointestinal tract is Nox1, which was long termed the "colon NADPH oxidase" [51][450][451]. Nox1 was also detected in the stomach under normal and disease conditions [452][453][454][455]. In addition to Nox1, Duox2 is expressed in the rectum, cecum and ascending colon [456][457][458], and Nox2 and Nox5 were detected in human gastric samples [454]. However, so far, Nox3 has not been detected nor associated with the gastrointestinal tract.

7. Role of Nox3 in Other Diseases

Plantinga et al. investigated genetic variants associated with susceptibility to agranulocytosis [459]. Agranulocytosis is defined as a reduced concentration of granulocytes in peripheral blood (<500 granulocytes/mL blood) [460][461]. Agranulocytosis can be induced by various factors, such as anti-psychotic drugs [462] or antibiotics [463][464], but is also observed in rare events (0.1–0.35%) in patients during treatment with thionamides to medicate hyperthyroidism [465][466][467]. This anti-thyroid drug-induced agranulocytosis (ATDAC) can be a life-threatening condition [461][468], especially after the usage of higher doses of anti-thyroid drugs [469]. During the conducted GWAS of Plantinga et al., two independent families and six patients with Graves' disease (GD) that developed ATDAC during treatment were analyzed. In 7 out of 11 GD-positive ATDAC patients, a variant of the *NOX3* gene were identified. The group reported that the *NOX3* gene variants p.Asn8Ser, p.Ala198Thr and p.Arg100Ile were absent in ATDAC-negative GD patients and were not detected in previous genetic screens for predisposition to GD [470][471]. Notably, all variants were located in regions of the membrane-spanning α-helices of the Nox3 protein.

CO poisoning is a consequence of malfunctioning oxygen supply due to carboxyhemoglobin forming in red blood cells [472][473]. The subsequent hypoxia leads to damage in various brain regions, such as the hippocampus or the striatum [474]. However, several research groups have suggested that hypoxia alone cannot be addressed as solely responsible for the brain damage. The involvement of various ROS subspecies has been discussed by Hara et al. and others as possible damage-inducing molecules in this context [475][476][477][478][479]. A previous study already detected increased Duox2 mRNA after CO exposure (3000 ppm, 40 min) in the rat striatum [480], but no mRNA of other Nox isoforms was detected. Hara et al. revised their findings [481] and used their well-established rat model in which CO exposition (1000 ppm or 3000 ppm) [476][482][483] simulates CO poisoning and brain damage [477][484]. The group found a small increase in Nox3 mRNA, while Nox1, Nox2 and Nox4 remained unchanged.

Mikkola et al. performed a GWAS for identification of new gene loci associated with canine hip dysplasia [485]. This canine skeletal disease is a hereditary disorder [486][487] of which the severity varies based on genetic variations [488][489][490] and the dog breed [489][491][492]. The group analyzed 750 German shepherd dogs and identified three new genetic loci associated with this disease. One of these newly identified loci is located on chromosome 1 in an intergenic position between the *NOX3* gene and the *ARDI1B* gene. The group identified the SNP BICF2P468585, which showed the strongest association with the disease and which was located approximately 196 kilobases upstream from the *NOX3*

gene. Another detected SNP, BICF2S23248027 (also termed rs21911799), was located in the intron between the exons 9 and 10 of the *NOX3* gene.

During a study which investigated the therapeutic effects of Dimethyl fumarate (DMF) on relapsing-remitting multiple sclerosis (RRMS) in 564 participants, Carlströem et al. detected a SNP in the *NOX3* gene associated with a better DMF treatment outcome [493]. RRMS is an autoimmune disease characterized by the entry of immune cells into the central nervous system (CNS), which leads to pro-inflammatory tissue damage accompanied by neurological dysfunction [494][495]. Like in many other autoimmune pathological settings [496][497], oxidative distress was reported to be a modulating factor in RRMS [498][499][500]. DMF (Tecfidera®) is one of the most prescribed substances for patients that suffer from RRMS [494][501]. The identified SNP rs6919626 in the *NOX3* gene allele was associated with a probability of an insufficient DMF treatment response. The group stimulated CD14+ monocytes isolated from patients with the identified *NOX3* SNP rs6919626 with *Escherichia coli* in vitro and detected a reduced total cellular ROS production. This study suggested for the first time a possible link between Nox3-derived ROS and MS disease outcome and treatment.

Li et al. analyzed thyroid tissue samples from 11 patients who suffered from tertiary hyperparathyroidism (THPT) [502]. Hyperparathyroidism manifests itself by an enlargement of the parathyroid gland, increased levels of circulating parathyroid hormone, as well as disturbed bone and mineral metabolism [503][504]. THPT develops during chronic kidney diseases and differs from hyperparathyroidism in an uncontrolled hypercalcemia, i.e., excessive Ca^{2+} levels in the blood [505]. Since the molecular mechanisms of this process remain largely unknown, Li and colleagues investigated this topic by analyzing blood and thyroid tissue samples from 16 Chinese THPT patients. The group used whole-exome sequencing for the detection of SNPs and insertions or deletions variants. During the screen, 17,401 mutations (6690 missense variants, 3078 frameshift variants, 2005 stop-gained variants and 1630 synonymous variants) were detected in THPT patient samples. From this data set, a further driver mutation analysis identified 179 mutated genes, one of them being the *NOX3* gene. Expression quantification by qRT-PCR additionally revealed decreased levels of *NOX3* gene mRNA in thyroid gland samples from THPT patients.

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