The past decade has witnessed an explosion of knowledge regarding how mitochondrial dysfunction may translate into ageing and disease phenotypes, as well as how it is modulated by genetic and lifestyle factors. In addition to energy production, mitochondria play an important role in regulating apoptosis, buffering calcium release, retrograde signaling to the nuclear genome, producing reactive oxygen species (ROS), participating in steroid synthesis, signaling to the immune system, as well as controlling the cell cycle and cell growth. Impairment of the mitochondria may be caused by mutations or deletions in nuclear or mitochondrial DNA (mtDNA). Hallmarks of mitochondrial dysfunction include decreased ATP production, decreased mitochondrial membrane potential, swollen mitochondria, damaged cristae, increased oxidative stress, and decreased mitochondrial DNA copy number.

Dysfunctional mitochondria have been implicated in ageing and in several diseases, many of which are age-related, including mitochondrial diseases, cancers, metabolic diseases and diabetes, inflammatory conditions, neuropathy, and neurodegenerative diseases such as Alzheimer’s, Parkinson’s, and Huntington’s disease. Additionally, a possible link between mitochondrial metabolism and the ubiquitin-proteasome and autophagy-lysosome systems is emerging as a novel factor contributing to the progression of several human diseases. The purpose of the Special Issue “Mitochondrial Dysfunction in Ageing and Diseases” published in the *International Journal of Molecular Sciences* [1] was to capture reviews, perspectives, and original research articles to address the progress and current standing in the vast field of mitochondrial biology. A total of 21 papers consisting of 17 reviews and 4 articles have been published as part of the Special Issue as detailed in Table 1. Topics included range from mitochondrial function, cell signaling, and protein homeostasis to disorders and diseases where mitochondrial dysfunction are implicated, such as metabolic diseases, ageing, several age-related diseases, as well as cancer. Various therapies to counteract mitochondrial dysfunction are also discussed.

### Table 1. Summary of papers in the Special Issue, arranged by topic as pertaining to mitochondrial dysfunction.

| Authors         | Title                                                                 | Topics/Keywords                              | Type     |
|-----------------|----------------------------------------------------------------------|----------------------------------------------|----------|
| Ahmed et al. [2] | Genes and Pathways Involved in Adult Onset Disorders Featuring Muscle Mitochondrial DNA Instability | mtDNA Maintenance; Mitochondrial Disorders | Review   |
| Arnould et al. [3] | Mitochondria Retrograde Signaling and the UPRmt: Where Are We in Mammals? | Unfolded Protein Response; Cell Signaling     | Review   |
| Authors            | Title                                                                 | Topics/Keywords                                      | Type     |
|--------------------|----------------------------------------------------------------------|------------------------------------------------------|----------|
| Ding et al. [4]    | Borrowing Nuclear DNA Helicases to Protect Mitochondrial DNA         | DNA Replication and Repair; Diseases                | Review   |
| Ross et al. [5]    | Mitochondrial and Ubiquitin Proteasome System Dysfunction in Ageing and Disease: Two Sides of the Same Coin? | Ageing and Age-Related Diseases; Ubiquitin; Proteasome | Review   |
| Crescenzo et al. [6]| Skeletal Muscle Mitochondrial Energetic Efficiency and Aging         | Ageing; Skeletal Muscle                               | Review   |
| Tricarico et al. [7]| Mevalonate Pathway Blockade, Mitochondrial Dysfunction and Autophagy: A Possible Link | Cholesterol Synthesis; Autophagy; Inflammation       | Review   |
| Zhang et al. [8]   | Autophagy as a Regulatory Component of Erythropoiesis                 | Autophagy; Erythroid Differentiation                 | Review   |
| Mikhed et al. [9]  | Mitochondrial Oxidative Stress, Mitochondrial DNA Damage and Their Role in Age-Related Vascular Dysfunction | Ageing; Cardiovascular Diseases; Oxidative Stress    | Review   |
| Vaitkus et al. [10]| Thyroid Hormone Mediated Modulation of Energy Expenditure            | Thyroid Hormone; Energy Expenditure                  | Review   |
| Forini et al. [11] | Low T3 State Is Correlated with Cardiac Mitochondrial Impairments after Ischemia Reperfusion Injury: Evidence from a Proteomic Approach | Thyroid Hormone; Cardiac Ischemia and Reperfusion; Proteomics | Article  |
| Forini et al. [12] | Mitochondria as Key Targets of Cardioprotection in Cardiac Ischemic Disease: Role of Thyroid Hormone Triiodothyronine | Cardiac Ischemia; Thyroid Hormone; Cardioprotection  | Review   |
| Cimolai et al. [13]| Mitochondrial Mechanisms in Septic Cardiomyopathy                    | Septic Cardiomyopathy; Mitophagy                     | Review   |
| Baburamani et al. [14]| Mitochondrial Optic Atrophy (OPA) 1 Processing Is Altered in Response to Neonatal Hypoxic-Ischemic Brain Injury | Hypoxia-Ischemia; Brain Injury                       | Article  |
| Luo et al. [15]    | Mitochondria: A Therapeutic Target for Parkinson’s Disease?          | Parkinson’s Disease; Mitochondrial Dynamics         | Review   |
| Kim et al. [16]    | The Role of Mitochondrial DNA in Mediating Alveolar Epithelial Cell Apoptosis and Pulmonary Fibrosis | Pulmonary Fibrosis; Sirtuins                         | Review   |
| Pagano et al. [17] | Current Experience in Testing Mitochondrial Nutrients in Disorders Featuring Oxidative Stress and Mitochondrial Dysfunction: Rational Design of Chemoprevention Trials | Mitochondrial Co-Factors as Therapeutics             | Review   |
| Modica-Napolitano et al. [18]| Treatment Strategies that Enhance the Efficacy and Selectivity of Mitochondria-Targeted Anticancer Agents | Cancer; Combination Therapy                         | Review   |
| Zhang et al. [19]  | Targeting Mitochondrial Function to Treat Quiescent Tumor Cells in Solid Tumors | Cancer; Cancer Therapies                             | Review   |
| Kohno et al. [20]  | Mitochondrial Transcription Factor A and Mitochondrial Genome as Molecular Targets for Cisplatin-Based Cancer Chemotherapy | mtTFAM; Cancer Chemotherapy                          | Review   |
The Special Issue opens with three reviews describing aspects of the mitochondrial machinery in the context of maintaining homeostasis and disease [2–4]. Ding and Liu [4] together with Ahmed et al. [2] summarize the maintenance and replication of the mitochondrial genome, and discuss how DNA helicases and mtDNA instability affect integrity of the mtDNA, thus contributing to mitochondrial diseases and disorders. Mitochondrial retrograde signaling, specifically the mitochondrial unfolded protein response, involved in proteostasis is reviewed by Arnould et al. [3]. The next five papers review the interconnectedness of mitochondrial dysfunction and protein homeostasis in health, ageing, and diseases [5–9]. Ross et al. [5] discuss the interplay of mitochondrial dysfunction and impairment of the ubiquitin proteasome system in ageing and disease, and provide a hypothetical model to address the heterogeneity often described during ageing. The heterogeneity of skeletal muscle performance in ageing is examined by Crescenzino et al. [6], taking into account the diverse mitochondrial populations present in skeletal muscle. Tricarico et al. [7] focus on a possible link between mitochondrial dysfunction, defective protein prenylation, and the mevalonate pathway, crucial for cholesterol synthesis, with disease. Zhang et al. [8] describe under physiological and pathological conditions the modulators of autophagy that regulate erythropoiesis, a process during which mitochondria and other intracellular organelles are removed. The intersection of mtDNA damage and oxidative stress on age-related vascular dysfunction is presented by Mikhed et al. [9], with particular focus on nicotinamide adenosine dinucleotide phosphate (NADPH) oxidases.

We received several reviews and research articles implicating mitochondria in cardiovascular diseases and ischemia as well as cerebral hypoxia-ischemia [11–14]. Interestingly, a few of these contributions highlight the role of thyroid hormone [10–12]. Vaikus et al. [10] review the diverse effects that thyroid hormone has on mitochondria and energy expenditure, including mitochondrial biogenesis and clinical correlates. Forini et al. [12] discuss possible thyroid hormone triiodothyronine (T3) supplementation to improve mitochondrial function in the context of ischemic heart disease. The same research group also present findings [11] indicating that low T3 levels are correlated with mitochondrial impairments following cardiac ischemia reperfusion injury. Mitochondrial dysfunction is also associated with septic cardiomyopathy, a complication of sepsis, which is a serious condition where the pathogenesis and underlying mechanisms remain unclear, as described by Cimolai et al. [13]. Findings discussed by Babiramani et al. [14] suggest that neonatal cerebral hypoxic-ischemia may alter mitochondrial dynamics, affecting optic atrophy 1 (OPA1). Impaired mitochondrial dynamics have also been described in neurodegenerative diseases, such as Parkinson’s disease (PD). Luo et al. [15] review recent literature that support the role of compromised mitochondrial dynamics, mitophagy, and mitochondrial import in PD, and also offer a list of potential therapeutics that target mitochondria. The review by Kim et al. [16] discusses the link between mitochondrial dysfunction and alveolar epithelial cell apoptosis in contributing to age-related lung diseases, as well as how sirtuin family members may constitute therapeutic candidates. Mitochondrial co-factors, such as α-lipoic acid, carnitine, and Coenzyme Q10 have been used to treat mitochondria-associated disorders and diseases, and the results of several clinical trials using these co-factors with and without antioxidants/herbal compounds are systematically presented by Pagano et al. [17].

A few contributions regarding the involvement of mitochondria in cancer and possible therapies were also received [18–21]. Ever since the “Warburg effect” was described nearly a century...
ago, mitochondria have been increasingly implicated in cancer biology. Extensive research has revealed notable differences between cancerous and healthy cells, such as altered mitochondrial size, shape, metabolic profiles, membrane potential, as well as elevated levels of mtDNA mutations, mitochondrial transcription factor A (TFAM), and oxidative stress [18,20]. Using these findings to exploit mitochondria, several promising anti-cancer treatments have been developed, but have unfortunately proven to have limitations [18–21]. Thus, researchers have recently explored alternative strategies as summarized in Modica-Napolitano and Weissig [18] as well as targeting specific microenvironments within tumors as discussed by Zhang et al. [19]. Moreover, the mechanisms by which cancer cells develop drug-resistance are currently being investigated, as reviewed by Kohno et al. [20], and possible means to mitigate the side effects of anti-cancer therapies are also being studied by Wang et al. [21]. Collectively, these contributions focus on mitochondrial mechanisms as an avenue to reveal possible novel interventions in order to combat cancer.

Lastly, but certainly not of least importance, recent studies of the role of mitochondrial function in fertility and oocyte quality have been extensive. Research by Wang et al. [22] demonstrates that androgen receptor knockout mice have poor oocyte maturing rates, impaired ATP production in granulosa cell mitochondria, and impaired mitochondria biogenesis. Additional research is needed to better understand how mitochondrial function may affect fertility and fecundity in order to develop therapeutic approaches.

Overall, the 21 contributions published in the Special Issue illustrate how essential mitochondria are to overall health and success of an organism. The involvement of mitochondria in several biological disciplines, diseases, and disorders, ranging from cancer biology, metabolism, and proteostasis to neurodegenerative and cardiovascular diseases is a testament to their importance and fundamental contributions. We would like to thank all of the authors who contributed their work to the Special Issue. The main objective was to provide ample breadth and depth to depict the interconnectedness of mitochondrial function in ageing and mitochondrial-associated diseases. While the underlying mechanisms linking impaired mitochondria with the ageing process and disease states remain incompletely elucidated, the overall field of mitochondrial biology has made leaps and bounds in only the past two decades. Based on these breakthroughs, new “mito-research” platforms have emerged; for example, mitochondrial function in fertility or in stem cell niches. We remain hopeful that harnessing the power of the mitochondrial network will help us stay healthy.

Acknowledgments: The Foundation for Geriatric Diseases at Karolinska Institutet (G.C.), Karolinska Institutet Research Foundations (G.C.), Loo och Hans Ostermans Foundation for Medical Research (G.C.), the Swedish Society for Medical Research (G.C., J.M.R.), Swedish Brain Power (G.C., J.M.R.), the Swedish Research Council (537-2014-6856; J.M.R.), the Swedish Brain Foundation (J.M.R.), Swedish Lundbeck Foundation (J.M.R.), and Konung Gustaf V:s och Drottning Victorias Frimurarestiftelse (J.M.R.).

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Special issue “mitochondrial dysfunction in ageing and diseases”. Int. J. Mol. Sci. 2016, 17, 711.
2. Ahmed, N.; Ronchi, D.; Comi, G.P . Genes and pathways involved in adult onset disorders featuring muscle mitochondrial DNA instability. Int. J. Mol. Sci. 2015, 16, 18054–18076. [CrossRef] [PubMed]
3. Arnould, T.; Michel, S.; Renard, P. Mitochondria retrograde signaling and the UPR mt: Where are we in mammals? Int. J. Mol. Sci. 2015, 16, 18224–18251. [CrossRef] [PubMed]
4. Ding, L.; Liu, Y. Borrowing nuclear DNA helicases to protect mitochondrial DNA. Int. J. Mol. Sci. 2015, 16, 10870–10887. [CrossRef] [PubMed]
5. Ross, J.M.; Olson, L.; Coppotelli, G. Mitochondrial and ubiquitin proteasome system dysfunction in ageing and disease: Two sides of the same coin? Int. J. Mol. Sci. 2015, 16, 19458–19476. [CrossRef] [PubMed]
6. Crescenzo, R.; Bianco, F.; Mazzoli, A.; Giacco, A.; Liverini, G.; Iossa, S. Skeletal muscle mitochondrial energetic efficiency and aging. Int. J. Mol. Sci. 2015, 16, 10674–10685. [CrossRef] [PubMed]
7. Tricarico, P.M.; Crovella, S.; Celsi, F. Mevalonate pathway blockade, mitochondrial dysfunction and autophagy: A possible link. *Int. J. Mol. Sci.* 2015, 16, 16067–16084. [CrossRef] [PubMed]

8. Zhang, J.; Wu, K.; Xiao, X.; Liao, J.; Hu, Q.; Chen, H.; Liu, J.; An, X. Autophagy as a regulatory component of erythropoiesis. *Int. J. Mol. Sci.* 2015, 16, 4083–4094. [CrossRef] [PubMed]

9. Mikhed, Y.; Daiber, A.; Steven, S. Mitochondrial oxidative stress, mitochondrial DNA damage and their role in age-related vascular dysfunction. *Int. J. Mol. Sci.* 2015, 16, 15918–15953. [CrossRef] [PubMed]

10. Vaitkus, J.A.; Farrar, J.S.; Celi, F.S. Thyroid hormone mediated modulation of energy expenditure. *Int. J. Mol. Sci.* 2015, 16, 16158–16175. [CrossRef] [PubMed]

11. Forini, F.; Ucciferri, N.; Kusmic, C.; Nicolini, G.; Cechettini, A.; Rocchiccioli, S.; Citti, L.; Iervasi, G. Low T3 state is correlated with cardiac mitochondrial impairments after ischemia reperfusion injury: Evidence from a proteomic approach. *Int. J. Mol. Sci.* 2015, 16, 26687–26705. [CrossRef] [PubMed]

12. Forini, F.; Nicolini, G.; Iervasi, G. Mitochondria as key targets of cardioprotection in cardiac ischemic disease: Role of thyroid hormone triiodothyronine. *Int. J. Mol. Sci.* 2015, 16, 6312–6336. [CrossRef] [PubMed]

13. Cimolai, M.C.; Alvarez, S.; Bode, C.; Bugger, H. Mitochondrial mechanisms in septic cardiomyopathy. *Int. J. Mol. Sci.* 2015, 16, 17763–17778. [CrossRef] [PubMed]

14. Baburamani, A.A.; Hurling, C.; Stolp, H.; Sobotka, K.; Gressens, P.; Hagberg, H.; Thornton, C. Mitochondrial optic atrophy (OPA) 1 processing is altered in response to neonatal hypoxic-ischemic brain injury. *Int. J. Mol. Sci.* 2015, 16, 22509–22526. [CrossRef] [PubMed]

15. Luo, Y.; Hoffer, A.; Hoffer, B.; Qi, X. Mitochondria: A therapeutic target for Parkinson’s disease? *Int. J. Mol. Sci.* 2015, 16, 20704–20730. [CrossRef] [PubMed]

16. Kim, S.-J.; Cheresh, P.; Jablonski, R.P.; Williams, D.B.; Kamp, D.W. The role of mitochondrial DNA in mediating alveolar epithelial cell apoptosis and pulmonary fibrosis. *Int. J. Mol. Sci.* 2015, 16, 21486–21519. [CrossRef] [PubMed]

17. Pagano, G.; Aiello Talamanca, A.; Castello, G.; Cordero, M.D.; d’Ischia, M.; Gadaleta, M.N.; Pallardó, F.V.; Petrović, S.; Tiano, L.; Zatterale, A. Current experience in testing mitochondrial nutrients in disorders featuring oxidative stress and mitochondrial dysfunction: Rational design of chemoprevention trials. *Int. J. Mol. Sci.* 2014, 15, 20169–20208. [CrossRef] [PubMed]

18. Modica-Napolitano, J.S.; Weissig, V. Treatment strategies that enhance the efficacy and selectivity of mitochondria-targeted anticancer agents. *Int. J. Mol. Sci.* 2015, 16, 17394–17421. [CrossRef] [PubMed]

19. Zhang, X.; de Milito, A.; Olofsson, M.H.; Gullbo, J.; D’Arcy, P.; Linder, S. Targeting mitochondrial function to treat quiescent tumor cells in solid tumors. *Int. J. Mol. Sci.* 2015, 16, 27313–27326. [CrossRef] [PubMed]

20. Kohno, K.; Wang, K.-Y.; Takahashi, M.; Kurita, T.; Yoshida, Y.; Hirakawa, M.; Harada, Y.; Kuma, A.; Izumi, H.; Matsumoto, S. Mitochondrial transcription factor A and mitochondrial genome as molecular targets for cisplatin-based cancer chemotherapy. *Int. J. Mol. Sci.* 2015, 16, 19836–19850. [CrossRef] [PubMed]

21. Wang, Z.; Wang, J.; Xie, R.; Liu, R.; Lu, Y. Mitochondria-derived reactive oxygen species play an important role in Doxorubicin-induced platelet apoptosis. *Int. J. Mol. Sci.* 2015, 16, 11087–11100. [CrossRef] [PubMed]

22. Wang, R.-S.; Chang, H.-Y.; Kao, S.-H.; Kao, C.-H.; Wu, Y.-C.; Yeh, S.; Tseng, C.-R.; Chang, C. Abnormal mitochondrial function and impaired granulosa cell differentiation in androgen receptor knockout mice. *Int. J. Mol. Sci.* 2015, 16, 9831–9849. [CrossRef] [PubMed]