

AGING

From Fundamental Biology to Societal Impact

Contents

ist	of co	ontributors	XXI
or	ewon	d .	XXXV
re	face		xxxvii
56	ecti	on 1 The societal burden of aging	
١.	Glo	bal aging and health determinants in a changing world	3
	Mig	uel Padeiro, Paula Santana and Marcus Grant	
	1.1	Introduction	3
	1.2	As your allowed and a confinement from appealing and the street and	3
	1.2	1.2.1 Global patterns and projections	3
		1.2.1 Global patterns and projections 1.2.2 Multiscale intraregional variations of the aging process	8
	13	Environmental health in later life	10
	1.5	1.3.1 From successful aging to the role of place and inequities	10
		1.3.2 How environment affects physical health in old age	11
		1.3.3 The subjective experience of place: place attachment and residential normalcy	15
	14	Global stressors in a changing world	17
	1.7	1.4.1 Welfare state and neoliberalism	17
		1.4.2 Climate change and health in old age	18
		1.4.3 Migrations and health in old age	19
		1.4.4 Discrimination as a health issue for older persons	21
	1.5	Conclusion	21
		nowledgments	22
		erences	22
2.	Fla	gship initiatives for healthy living and active aging in Europe:	
	the	European Innovation Partnership on Active and Healthy Ageing and	
	the	Reference Sites	31
	Vice	o O. Malva, Daan Bultje, Vicente Traver-Salcedo, Ana Maria Carriazo, Maddalena Illario, enzo De Luca, Lucyna A. Wozniak, Jean Bousquet, Nick Guldemond, Inês Costa, ena Canhão, Elísio Costa and John Farrel	
	2.1	Demographic changes and aging	31
	2.2	The European Innovation Partnership on Active and Healthy Ageing	32
		2.2.1 European Innovation Partnership on Active and Healthy Ageing cross-cutting	
		initiatives	34
	2.3	Reference sites—case studies	34

		2.3.1 Ageing@Coimbra Reference Site	34
		2.3.2 The Healthy Ageing Network Northern Netherlands	36
		2.3.3 Valencia region Reference Site	37
		2.3.4 Andalusia Reference Site	38
		2.3.5 The Lodz4Generations Reference Site	39
		2.3.6 Campania Reference Site (ProMIS network)	41
		2.3.7 MACVIA-France Reference Site	42
	2.4	Reference Site Collaborative Network	42
	2.5	Transition from Horizon 2020 to Horizon Europe—the role of IN-4-Active and	
		Healthy Ageing	44
	2.6	Future perspectives	45
	Ackn	owledgment Programme British B	46
	Refer	ences	47
3.	-	ng in Africa, challenges and opportunities—the particular case of	1.5
	Cab	o Verde	49
		ando J. Regateiro, António Correia e Silva, António M.D. Brehm, Dario D. Reis,	
		a S.R.C. Semedo, Edith Pereira, Hélder Spínola, Jorge N. Barreto,	
	Juan	e M. Nascimento, Maria L. Lima Mendonça and Maria Natalina L. Silva	
	3.1	Aging in Africa and West African Region	49
	3.2	Geography and climate of Cabo Verde	50
	3.3	Cabo Verde, the historical healthy islands	51
	3.4	Epidemiology of slave society	51
	3.5	Cabo Verde Famines	52
	3.6	Cabo Verdean population genetics	53
	3.7	Age pyramid of Cabo Verdean population	55
	3.8	Urbanization of Cabo Verdean population	55
	3.9	Aging and the emergence of a new demographic model	57
	3.10	Elderly in Cabo Verde	58
	3.11	Health and national health service—philosophy, structures, and budget	59
	3.12	Healthy and active aging policies	60
	3.13	Aging and poverty	60
		Aging and gender	61
		To a healthy living and active aging in Cabo Verde—the future	62
	Refer	ences	63
1	Class	chin initiatives to provent and treat dishates as a hurden of	
4.	2018 123 T	ship initiatives to prevent and treat diabetes as a burden of tern societies	67
			07
	rete	r Goulden and Eugenia Carvalho	
		Introduction	67
		4.1.1 Demographics of diabetes and prediabetes	68

				Contents
		4.1.2	Healthcare literacy and numeracy	68
		4.1.3	Food insecurity and dietary quality	69
		4.1.4	Community engagement	69
	4.2	Impad	ct of research: prediabetes	70
		07000000	The diabetes prevention program study	70
		4.2.2	The finnish diabetes prevention study	71
	4.3	Lifesty	vle interventions	71
		4.3.1	The national diabetes prevention program	71
			Exercise	72
		4.3.3	Pharmacologic therapy in prediabetes	72
	4.4	Impad	ct of research: diabetes	73
		4.4.1	Diabetes self-management education	73
	4.5		nary and conclusions	74
		erences		75
5.			ning factors on active aging in Asia and Oceania: a systematic	Section
	rev	iew		77
	Yue	zhong	Liu, Rakhi Verma and Yin-Leng Theng	
	5.1	Introd	duction	- 77
	5.2		odology	78
			Population aging in Asia and Oceania	78
			Data sources and search strategies	78
		5.2.3		79
		5.2.4		79
			Data extraction	80
	5.3	Result		81
	0.0		Exergaming/active video games	81
		5.3.2	Health wearables and activity trackers	85
		5.3.3	Smartphones	85
			Web-based programs	96
	5.4		ssion and concluding remarks	105
		erences		106
_			 Stander of Assemblie Sentence Agency and Assembly Assembly Sentence (Assembly Sentence) 	
6.			living and active aging in Latin America and the Caribbean s: biological, demographic, and epidemiological challenges	113
			pelho-Filho, Reinaldo B. Oriá, Karla C. Giacomin, Gerly A.C. Brito, Marcos Santos, aran, Manoela Heringer, Deiziane V.S. Costa, Ronaldo P. Dias and Vivaldo M. Neto	JEA DA
	6.1	Introd	duction	113
	6.2		ographic and epidemiological changes in the Latin America and the Caribbean	115
		CULIII	W152	

vii

	6.3	Age-related biological changes and diseases in the context of Latin America and the Caribbean countries	119
		6.3.1 Immunosenescence and infectious diseases	121
		6.3.2 Age-related intestinal microbiota changes: the role in neurodegenerative and metabolic diseases	126
		6.3.3 Common age-related diseases: cancer, vascular diseases, diabetes and neurodegenerative disorders	128
	6.4	Health and social initiatives for the promotion of healthy living and active aging	133
		6.4.1 Age-friendly initiatives	133
		6.4.2 Labor force participation and active aging	135
	6.5	Selected health issues among older people: evidence from long-term cohorts in Latin America	137
	6.6	Conclusion	150
	Refe	rences	150
Se	ectio	on 2 The biology of aging	
7.		ntification of metrics of molecular and cellular resilience in nans and animal models	161
	Felip	pe Sierra	
	7.1	Biomedicine is focused on disease, not health	161
	7.2	Comorbidities are the prevailing characteristic of older age	162
	7.3	Chronological versus physiological age	163
	7.4	Linking aging to disease: geroscience principles	164
	7.5		166
	7.6		167
	7.7	Measuring molecular resilience	169
	7.8	We need to develop resilience metrics in animal models	171
	7.9		172
	7.10	Conclusions	172
	Refe	rences	173
8.	A m	netabolic and mitochondrial angle on aging	175
	Mag	I. Duarte, Izabela Sadowska-Bartosz, Agnieszka Karkucinska-Wieckowska, dalena Lebiedzinska-Arciszewska, Carlos M. Palmeira, Anabela P. Rolo, Yaschar Kabiri,	
		para Zavan, Paolo Pinton, Fernanda Borges, Hans Zischka, John G. Jones, egorz Bartosz, Paulo J. Oliveira and Mariusz R. Wieckowski	
	Abb	reviations	175
		Aging and longevity: revisiting the evolutionary perspectives and controversies	177
	8.2	Aging and longevity: challenging the traditional views for mitochondrial-derived oxidative stress	178
		WE THAT WAS A WAY WAY.	17.0

		Contents
	8.3 Changes of mitochondrial function and structure associated with aging	181
	8.3.1 Oxidative phosphorylation and aging	181
	8.3.2 Mitochondrial morphology and dynamics in aging	184
	8.4 A metabolic angle on aging	185
	8.4.1 Carbohydrate metabolism and aging	185
	8.4.2 Lipid metabolism and aging	186
	8.4.3 Protein metabolism and aging	187
	8.4.4 Nutrient metabolism and caloric restriction	188
	8.5 Oxidative stress and aging	188
	8.5.1 Reactive oxygen species and their reactions	188
	8.5.2 Reactive oxygen species as the cause of aging	192
	8.5.3 Antioxidant defense in aging	193
	8.5.4 Mitochondrial free radical theory of aging	196
	8.5.5 Accumulation of reactive oxygen species-induced damage with agin	ng 199
	8.5.6 Age-related oxidative modifications of mitochondria	202
	8.6 Potential strategies against aging to increase longevity	208
	8.6.1 Metabolic control-related approaches	208
	8.6.2 Mitochondria-related antioxidant approaches	216
	8.7 Conclusions	225
	Acknowledgments	225
	References	225
9.	Intercellular communication and aging	257
	Teresa M. Ribeiro-Rodrigues, George Kelly, Viktor I. Korolchuk and Henrique	Girao
	9.1 Importance of intercellular communication	257
	9.2 The defining features of senescence	258
	9.3 The mechanisms responsible for the induction of cellular senescence	259
	9.4 Senescence associated secretory phenotype	260
	9.5 Intercellular communication mediated by gap junctions and connexin cha	nnels 261
	9.6 Intercellular communication mediated by tunneling nanotubes	264
	9.7 Intercellular communication mediated by extracellular vesicles	265
	9.8 Concluding remarks	269
	Acknowledgments	269
	References	269
10.	. Genomic instability and aging	275
	Zhiquan Li, Sharath Anugula and Lene Juel Rasmussen	
	10.1 Introduction	275
	10.2 DNA strand breakage-induced genomic instability	277
	10.3 Replication-induced genomic instability	277

ix

	10.3.1 Replication stress	211
	10.3.2 Translesion DNA synthesis	278
	10.3.3 Mismatch repair	279
10.4	Transcription-induced genomic instability	279
	10.4.1 Transcription-coupled repair	280
	10.4.2 Transcription-replication conflicts =	280
10.5	Nucleotide pools	280
10.6	Mitochondrial functions in genomic integrity	281
	10.6.1 Mitochondrial oxidative stress	281
	10.6.2 FOXO in oxidative DNA damage response	282
	10.6.3 Mitochondrial genome maintenance	282
	10.6.4 Mitochondrial dysfunction	283
	10.6.5 Mitophagy	283
10.7	Genomic instability in health and disease	284
	10.7.1 Longevity	284
	10.7.2 Progeroid syndromes	285
	10.7.3 Cancer	286
	10.7.4 Neurodegeneration	286
10.8	Aging interventions activating DNA repair	286
	10.8.1 Exercise	286
	10.8.2 Dietary restriction	287
	10.8.3 Nicotinamide adenine dinucleotide	287
10.9	Conclusion and future perspectives	288
Ackn	owledgments	288
Refer	ences	288
11. Telo	meres and cell homeostasis in aging	297
Stella	a Victorelli and João F. Passos	
11.1	What is cellular senescence	297
11.2	Link between cell senescence and telomeres	297
11.3	Critically short telomeres activate a DNA damage response and senescence	298
11.4	Telomere dysfunction can occur in a length-independent manner	299
11.5	Mechanisms by which stress accelerates telomere dysfunction	.30
11.6	Telomere-associated DNA damage response foci accumulate during aging and	200
Barrie	disease	303
Refer	ences	300
12. Cellu	ular senescence during aging	311
Thon	nas von Zglinicki	
12.1	Cell senescence is a complex stress response	31
12.2	The building blocks of the senescent phenotype	314

		Contents
	12.2.1 Telomeres and the DNA damage response	314
	12.2.2 Senescence-associated secretory phenotype	316
	12.2.3 Senescence-associated mitochondrial dysfunction	317
	12.2.4 Nutrient signaling	318
	12.2.5 Autophagy/mitophagy	318
	12.2.6 Epigenetic reprogramming	320
12.3	Senescence during aging in vivo	320
	12.3.1 Senescence in postmitotic cells	321
	12.3.2 Senescent cell bystander effects	321
12.4	Senolytics and senostatics as anti-aging interventions	322
	12.4.1 Senolytics	322
	12.4.2 Senostatics	325
12.5	Conclusion	326
Refer	ences	326
13. The	epigenetics of aging	333
	nasios Metaxakis, Ilias Gkikas and Nektarios Tavernarakis	0.21
13.1	Introduction	333
13.2	Epigenetic alterations and aging	334
13.2	13.2.1 Histone depletion	334
	13.2.2 Non-canonical histone variants	335
	13.2.3 Histone acetylation	335
	13.2.4 Histone methylation	336
	13.2.5 ATP-dependent chromatin remodeling	337
	13.2.6 DNA methylation	338
	13.2.7 Non-coding RNA molecules	340
13.3		341
	13.3.1 Cancer and epigenetics	341
	13.3.2 Neuronal diseases and epigenetics	343
	13.3.3 Cardiovascular disease and epigenetics	344
13.4	Conclusions	345
Ackn	owledgment	347
	lict of interest	347
Refer	rences	347
14. Disr	upted cellular quality control mechanisms in aging	359
Crist	ina Carvalho, Joana F. Pires, Paula I. Moreira and Nuno Raimundo	
14.1	Aging: is it a programmed fate and/or an error accumulation?	359
14.2	Autophagy: an evolutionarily conserved process	360
14.3	Role of autophagy in aging: what can go wrong?	364

χi

	14.4	The chase for "eternal youth": can autophagy-directed interventions be the much-desired youth elixir?	366
	145	Going down the rabbit hole: how lysosomes modulate longevity pathways	370
		Partners in crime: mitochondria and lysosomes need each other	373
	Refere		374
	Heren		2551
15.	Sten	cells, fitness, and aging	385
		na Kitaeva, Andrey Kiyasov, Albert Rizvanov, Catrin Rutland and	
		iya Solovyeva	
	15.1	Introduction	385
	15.2	Cell fitness and cell competition	386
	15.3	Senescent mesenchymal stem cell phenotype	387
	15.4	The functionality changes in senescent mesenchymal stem cells	389
	15.5	The role of factors associated with aging	390
		15.5.1 Oxidative stress	390
	15.6	Genetic and epigenetic aspects	391
	15.7	Senescence-associated secretory phenotype and the microenvironment	393
	15.8	Therapeutic strategies to rejuvenate and increase fitness	395
	15.9	Conclusion	397
	Ackno	owledgments	398
	Refere	ences	398
16.	Prog	ramming of early aging	407
		na P. Pereira, Luís F. Grilo, Renata S. Tavares, Rodrigo M. Gomes, Ramalho-Santos, Susan E. Ozanne and Paulo Matafome	
	16.1	Epidemiology of early life environment and adult aging—developmental ori of health, disease, and aging?	gins 407
	16.2	Early life nutrition and programming of adult aging and lifespan	408
		16.2.1 Prenatal malnutrition, longevity, and aging	408
		16.2.2 Can lactation and early life nutrition contribute to early aging?	410
	16.3	Mechanisms underlying early programming of aging	411
		16.3.1 Metabolic programming	411
		16.3.2 Early cellular miscommunication and cellular senescence	412
		16.3.3 Programming of genomic aging and epigenetic alterations	413
	16.4	Early programming of aging-related diseases	414
		16.4.1 Inflammaging	414
		16.4.2 Cognitive decline and dementia	415
		16.4.3 Aging-related neoplasia	416
		16.4.4 Cardiovascular aging	417
		16.4.5 Physical frailty	418

16.5	Transgenerational passage of the aging clock—reproductive cell plasticity an	d
	selection	419
16.6	Life Interventions to "Re-set the Clock"	421
	16.6.1 Nutrigenomics as a strategy to revert early life programming	421
	16.6.2 Running against aging—exercise as anti-aging "medicine"	422
16.7	Conclusion	423
Refe	rences	424
	on 3 Aging-related physiology, disease and	
preve	ntion of aging-related diseases	
17. Poly	pharmacy and medication adherence	435
	a Lavrador, Ana Cristina Cabral, Margarida Castel-Branco, el Vitoria Figueiredo and Fernando Fernandez-Llimos	
17.1	Adherence to therapy and medication management	435
	17.1.1 Definition and classification	435
	17.1.2 Assessment methodologies	437
	17.1.3 Interventions in medication nonadherence	439
17.2	Concept of polypharmacy	442
	17.2.1 Potentially inappropriate medication in the elderly	443
	17.2.2 Pharmacokinetic and pharmacodynamic changes in older people	444
17.3	Inappropriate polypharmacy management	446
	17.3.1 Implicit tools	447
	17.3.2 Explicit tools	447
17.4	Epilogue	451
Refe	rences	452
	v molecular imaging studies can disentangle disease mechanisms -related neurodegenerative disorders	in 455
	ardo R. de Natale, Heather Wilson, Chi Udeh-Momoh, Jamie K. Ford, los Politis and Lefkos T. Middleton	
18.1	Introduction	455
18.2	Molecular imaging of neuroinflammation	457
18.3		461
18.4		462
	18.4.1 Molecular tracers of amyloid and tau in vivo PET imaging	463
18.5		466
	18.5.1 Molecular imaging of cerebral hypometabolism	466
	18.5.2 Molecular imaging of brain functional connectivity	467

xiii

18.6	Imaging of iron accumulation	469
	Emerging mechanisms of neurodegeneration	471
1,14,15	18.7.1 Glymphatic system	471
	18.7.2 O-GLcNAc	472
18.8	Translational use of molecular imaging in neurodegenerative diseases	472
18.9	Conclusions	473
Refe	rences	474
		400
19. Phy	sical frailty	493
Yim	ing Pan and Lina Ma	
Abb	reviations	493
19.1	The concept of frailty	495
	19.1.1 Frailty as a biological syndrome	495
	19.1.2 Frailty as cumulative deficits	495
19.2	Frailty assessment	496
	19.2.1 Frailty measurement tools	496
	19.2.2 A two-step frailty measurement	496
19.3	The biology of frailty	496
	19.3.1 Chronic inflammation	497
	19.3.2 Hypothalamic-pituitary axis stress response dysfunction	499
	19.3.3 Endocrine dysregulation (dysfunctional hormone regulation)	500
	19.3.4 Metabolic imbalance	500
	19.3.5 Oxidative stress and mitochondrial dysfunction	501
	19.3.6 Genomic factors	502
	19.3.7 Metabolomic markers	503
	Animal models of frailty	50-
19.5	Interventions to attenuate frailty	500
	19.5.1 Pharmacological interventions	500
	19.5.2 Nonpharmacological interventions	500
	Conclusion	509
Refe	erences	509
20. The	e extracellular matrix in cardiovascular aging	523
	olinda Santinha, Andreia Vilaça, Alessandro Ori and Lino Ferreira	
	reviations	523
	Introduction Physiological alterations of the aged heart	52:
20.2	Physiological alterations of the aged heart 20.2.1 Aging induces functional and morphologic cardiac alterations	52:
20.3	20.2.1 Aging induces functional and morphologic cardiac alterations Young cardiac extracellular matrix	52
20.0	Tours cardio consecution insure	- F-

Contents

XV

	Itidimensional frailty as an outcome of biological aging: nunosenescence and inflammaging in the life course perspective	577
М. С	Cristina Polidori, Luigi Ferrucci and Claudio Franceschi	
22.1	Introduction	577
22.2		578
22.3		579
22.4		581
22.5	Concluding remarks and research outlook	583
Refe	rences	583
Furt	her reading	585
23. Ger	oscience: a unifying view on aging as a risk factor	587
Cris	tina Mas-Bargues, Aurora Román-Domínguez, Consuelo Borrás and José Viña	
23.1	Centenarians: a growing population	587
23.2	Morbidity compression in centenarians	587
23.3	Limits of human longevity	589
23.4	Exceptional aging "must-haves"	590
	23.4.1 Low-grade inflammation	590
	23.4.2 Genetic signature	591
	23.4.3 Fine-tuned apoptosis	592
	23.4.4 Stem cell pluripotency	593
	23.4.5 Healthy lifestyle	593
23.5	Exceptional homeostasis in exceptional aging	595
23.6	Centenarians beyond 120?	596
Refe	erences	596
Secti	on 4 The future and innovation in aging	
24. Agi	ng support with socially assistive robots	603
Jorg	ge Dias and João Sequeira	
24.1	Introduction	603
	24.1.1 Social robotics tools for demanding societies	605
	24.1.2 Where are we in social robotics?	605
24.2	Where is social robotics heading?	608
	24.2.1 Social robots for aging societies	609
	24.2.2 User behaviors under uncertainty—the bayesian user model	611
	24.2.3 Online knowledge integration using learning	613

		Contents
24.3	Results with a team of robots	614
24.4	User's attributes from distributed, asynchronous data	616
24.5	Collectively cluster users into distinguishable profiles	618
	Discussion	618
Ackn	owledgments	621
Refer	rences	621
25. Mac	hine learning in the context of better healthcare in aging	625
	e Henriques, Caio Ribeiro, Teresa Rocha, Simão Paredes, Paulo de Carvall I. Duarte, Alex A. Freitas, Teresa Cunha-Oliveira and Francisco B. Pereira	ho,
25.1	Introduction	625
25.2	Machine learning overview	626
25.3	A review of machine learning applications for aging research	628
25.4	Telemonitoring data mining for hearth failure management	629
	25.4.1 Heart failure condition	630
	25.4.2 Algorithms for heart failure management	631
	25.4.3 Experimental results	634
	25.4.4 Discussion	636
25.5	Machine learning for the English Longitudinal Study of Ageing	636
	25.5.1 A brief overview of random forest classifiers	637
	25.5.2 Preparing the English Longitudinal Study of Ageing-nurse data fo classification task	r the 637
	25.5.3 Computational results	639
25.6	Feature importance analysis	640
25.7	Conclusion	643
Refer	rences	643
	future of integrated care in aged individuals	649
Alex	andre Lourenço, Maja Furlan de Brito and Bárbara Gomes	
26.1	Introduction	649
26.2	The current model is more and more inadequate	650
26.3	The avoidable suffering	651
26.4		651
	26.4.1 Healthy aging and disease prevention	652
	26.4.2 Patient-centeredness and multimorbidity	653
	26.4.3 Dementia	655
	26.4.4 Palliative, end life, and bereavement care	656
	Key messages	658
Rofor	rences	658

xvii

27. Mov	ing fro	m reactive to preventive medicine	663	
Lina	Badimo	n, Teresa Padro and Gemma Vilahur		
27.1	Introdu	action	663	
27.2	Aging	and major chronic diseases	664	
		The mechanistic interplay between aging and age-related diseases. In the search		
		of evidence for preventive medicine		
	27.3.1	Immunosenescence and age-related chronic diseases	666	
	27.3.2	Epigenetic drift and age-related chronic diseases	667	
27.4	Age-re	Age-related diseases—prevention initiatives are in order		
27.5	Do we have preventive strategies for ameliorating age-related diseases?			
	27.5.1	Non-pharmacological approaches	668	
	27.5.2	Pharmacological interventions	669	
27.6	Cardio	vascular disease: the success of prevention	670	
	27.6.1	Hypertension: the most prevalent cardiovascular risk factor	670	
27.7	Low-de	ensity lipoproteins-cholesterol lowering: the lower, the better	672	
	27.7.1	The need to control the obesity pandemic	674	
	27.7.2	Primordial prevention: the sooner, the better	674	
27.8	Conclu	ding remarks	676	
		ed medicine: will it work for decreasing age-related morbidities? R. Martens, Devin Wahl and Thomas J. LaRocca	683	
			400	
28.1	Introdu		683	
28.2		cal perspective	683	
28.3		g aging with GeroScience	684	
		The biological hallmarks of aging	684 686	
20.4		A case for personalized aging	686	
		alized medicine for optimal longevity	687	
28.5		ing predictors of "biological aging"	687	
		Epigenetic clocks	688	
		Transcriptomics Matabalamics and proteomics	688	
		Metabolomics and proteomics The out microbioms	689	
20.6		The gut microbiome	690	
28.6		ng personalized medicine to GeroScience Personalized nutrition	691	
207			692	
20.7		nges and barriers to implementing personalized aging Minimizing the risk-benefit ratio	693	
	28.7.1	Minimizing the risk-benefit ratio Increasing diversity in clinical research	693	
	28.7.2	Increasing diversity in clinical research Improving adherence and accessibility	694	
		Innovation in clinical trial design	694	
	20.7.4	initiovation in clinical trial design	0,5	

		Contents	
	28.7.5 Ethical and policy concerns	696	
	28.7.6 Cross-disciplinary innovation	696	
28.8	Conclusion	696	
Refer	ences ences	697	
	rventions that target fundamental aging mechanisms: hs and realities	701	
Erin	O. Wissler Gerdes, Yi Zhu, Tamar Tchkonia and James L. Kirkland		
29.1	Introduction	701	
29.2	Pillars of aging	701	
29.3	Genomic instability	702	
	29.3.1 Telomere attrition	702	
	29.3.2 Epigenetic alterations	702	
	29.3.3 Loss of proteostasis	703	
	29.3.4 Deregulated nutrient sensing	703	
	29.3.5 Mitochondrial dysfunction	703	
	29.3.6 Cellular senescence	704	
	29.3.7 Stem cell exhaustion	705	
	29.3.8 Altered intercellular communication	705	
29.4	Unitary theory of fundamental aging processes	705	
29.5	Health span versus lifespan	705	
29.6	Myths and realities		
	29.6.1 Senolytics	707	
	29.6.2 Other pharmacological interventions	712	
	29.6.3 Behavioral/dietary interventions	714	
29.7	Clinical trials and treating disease	715	
	29.7.1 Safety; risk/benefit ratio	715	
	29.7.2 Combining or sequencing therapies	715	
	29.7.3 Translational geroscience network	716	
29.8	Conclusion	717	
Confi	ict of interest disclosure	717	
Refer	ences	718	
30. Bein	g a frail older person at a time of the COVID-19 pandemic	725	
Yaoh	ua Chen, Susanne Röhr, Berenice Maria Werle and Roman Romero-Ortuno		
30.1	Introduction		
	30.1.1 A minority of community-dwelling older adults are frail	725	
	30.1.2 Frailty in the time of a pandemic: the "measured" versus the "lived"	726	
30.2	The community perspective	727	
	30.2.1 COVID-19-related challenges in community-dwelling frail older people	728	

xix

	30.2.2	A glimpse of hope	730		
30	.3 The ho	The hospital perspective			
	30.3.1	Atypical presentations	732		
	30.3.2	Biological heterogeneity of the population of hospitalized older people	732		
	30.3.3	Ethical considerations	733		
	30.3.4	Optimization of the hospital environment and opportunities for in-hospital rehabilitation	734		
	30.3.5	Hospital-associated deconditioning and post-COVID-19 fatigue	735		
30		The nursing home perspective			
30).5 Resear	Research on COVID-19 treatments and service development perspectives			
30	0.6 Conclu	usions	739		
Co	Competing interest				
Fu	Funding				
Re	References				
31. A	ging: an	illustrated adventure	745		
Jo	ão Ramall	no-Santos and André Caetano			
			755		
Index					