Review

Recent developments and future perspectives in aging and macrophage immunometabolism

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Abstract: Aging is the strongest contributor to the development and severity of many chronic and infectious diseases, primarily through age-related increases in low-grade inflammation (inflammaging) and decreases in immune function (immunosenescence). Metabolic reprogramming in immune cells is a significant contributor to functional and phenotypic changes in these cells, but little is known about the direct effect of aging on immunometabolism. This review highlights several recent advances in this field, focusing on mitochondrial dysfunction, NAD+ metabolism, and therapeutic reprogramming in aged monocytes and macrophages. Perspectives on opportunities for future research in this area are also provided. Targeting immunometabolism is a promising strategy for designing therapeutics for a wide variety of age-related diseases.

Keywords: aging; immunometabolism; macrophage; monocyte; mitochondrial function; NAD+

1. Introduction

Biological aging is a physiological process which leads to progressive cellular dysfunction and ultimately to death. Additionally, aging is the greatest risk factor for the majority of chronic diseases in developed countries, including cancer, neurodegenerative disease, cardiovascular disease, and others [1]. Underlying these diseases is an age-related chronic inflammatory state, which has given rise to the term inflammaging [2]. In addition to increased rates of chronic diseases, older adults experience more severe outcomes during acute infections, as evidenced by the ongoing coronavirus disease-19 (COVID-19) pandemic [3,4] as well as by aging-related complications associated with
circulating influenza [5,6] and respiratory syncytial [7] viruses. Aging-associated immune dysfunction has been termed immunosenescence [8], and impaired function has been identified as an aging hallmark in essentially all immune cell types [9]. As such, elucidation of the biological mechanisms underlying inflammaging and immunosenescence is of major interest in the fields of biogerontology and geroscience.

In recent years, there has been an explosion of scientific interest in immunometabolism. It has become clear that cellular metabolic programs control many of the functional processes in the immune system, and likewise that metabolic reprogramming of these cells can alter their phenotype and function [10]. Simplistically, pro-inflammatory and initial pathogen response programs are generally mediated by a shift to glycolytic metabolism, while anti-inflammatory and immune memory responses are generally supported by oxidative metabolism. Additionally, several metabolic intermediates have been identified as critical regulators of immunometabolism, including succinate [11,12], fumarate [13], and itaconate [14,15]. As a burgeoning field, a thorough review of immunometabolism is beyond the scope of this paper, but I point readers seeking greater depth to several excellent recent comprehensive reviews [10,16–19].

Despite these advances, the effect of aging on cellular immunometabolism has been studied only in a limited capacity [16,20]. This is beginning to change, however, and the remainder of this review will focus on several recent advances in this area, and will outline areas ripe for continuing advances. This will be restricted to examining the effect of aging on innate immunometabolism in macrophages and monocytes, as this has been the core focus of my laboratory for the past 5 years.

2. Aging and mitochondrial dysfunction

Mitochondria are well known as the “powerhouses” of the cell, and they are the site of ATP production from the electron transport chain and GTP production from the TCA cycle in eukaryotic cells. Mitochondria are also critical to immune responses, as they are both the site of ATP production during anti-inflammatory processes (principally supported by oxidative phosphorylation (OXPHOS) [10]) and the site of the accumulation of TCA cycle intermediates (e.g., succinate [11,12,21]) which promote glycolytic reprogramming during pro-inflammatory processes. Mitochondrial dysfunction limits energy production in cells and is a hallmark of the aging process [22]. Therefore, the effect of age-related mitochondrial dysfunction in immune responses is of considerable interest.

Age related mitochondrial dysfunction occurs in the innate immune system as well. We have previously used Seahorse assays to observe that monocytes isolated from older adults have reduced mitochondrial respiratory capacity compared to monocytes isolated from younger adults [23]. Recently, Saare and colleagues have extended this finding in a notable paper published in Aging Cell [24]. In this, they replicate the finding of mitochondrial dysfunction in monocytes isolated from older adults. Additionally, RNA sequencing data are provided which demonstrate gene expression patterns suggesting reduced OXPHOS and increased glycolysis in aged monocytes. Monocytes from older adults also had increased levels of reactive oxygen species (ROS) and impaired inflammatory responses to lipopolysaccharide (LPS), the latter of which supports previous observations [25–28].

Saare et al. also reported an increased uptake of glucose by aged monocytes using 2-NBDG, which was considered to be reflective of increased glycolysis in these cells. However, 2-NBDG has recently been shown to be inappropriate as a measure of glucose uptake in immune cells [29,30],
which do not express the transporter GLUT2. Other studies have failed to find increased glycolysis in monocytes from older adults using Seahorse assays [27], and so the impact of aging on glucose metabolism in monocytes is still an open question.

3. Aging and NAD+ metabolism

Nicotinamide adenine dinucleotide (NAD+) is a central regulator of cellular metabolism, functioning as an electron carrier by accepting electrons via a reduction reaction to form NADH. This reaction is critical to glycolysis, OXPHOS, the TCA cycle, and other intrinsic cellular metabolic programs, thus the cellular supply of NAD+ is important for maintaining homeostasis. During aging, the endogenous supply of NAD+ is depleted [31], which is thought to drive cellular aging and senescence through disrupting cellular metabolism.

Recently, several important papers have described mechanisms by which NAD+ coordinates macrophage phenotype and function, as well as the effect of aging on these processes. Cameron and colleagues recently described in Nature Immunology [32] that pro-inflammatory macrophages upregulate the NAMPT-dependent NAD+ salvage pathway [33] to promote glycolytic metabolism and inflammation, as the NAMPT inhibitor FK866 inhibited extracellular acidification in Seahorse assays in LPS- and interferon-γ (IFN-γ) + LPS-polarized macrophages, and abrogated protein expression of various pro-inflammatory cytokines and cellular signaling markers in these cell types. Pro-inflammatory macrophages were also found to rapidly deplete their NAD+ stores, which was due to DNA damage caused by mitochondrial complex III-dependent ROS production in these cells during polarization/activation. DNA damage is a hallmark of the aging process [22], and so these findings may represent a mechanism whereby myeloid cells take on a chronic pro-inflammatory phenotype during the aging process.

In the same issue of Nature Immunology, Minhas and colleagues [34] utilized FK866 to block the NAD+ salvage pathway in quiescent macrophages, demonstrating that these cells utilize the kynurenine pathway to promote de novo NAD+ synthesis. Blocking this suppressed mitochondrial respiration, likely because NAD+ functions as a substrate for mitochondrial complex I in the electron transport chain. Additionally, inhibition of de novo NAD+ synthesis promoted a pro-inflammatory phenotype in both unstimulated and LPS-stimulated macrophages, and LPS itself suppressed the de novo NAD+ synthesis pathway through decreased expression of the enzyme QPRT. Minhas et al. then extended these findings to aging macrophages, demonstrating a reduction in QPRT expression that supported de novo NAD+ synthesis, mitochondrial respiration, and mitochondrial complex I and II activity.

Taken together, Cameron et al. [32] and Minhas et al. [34] suggest a shift from de novo NAD+ synthesis to NAD+ salvage in aging macrophages which promotes a pro-inflammatory phenotype. Covarrubias and colleagues recently published a paper in Nature Metabolism [35] which supports this. Here, they demonstrate that pro-inflammatory macrophages consume NAD+ through increasing expression of NAD-consuming enzymes including CD38. As with Cameron et al. [32], Covarrubias et al. [35] demonstrated increased salvage pathway activity in LPS-polarized macrophages. Interestingly, Covarrubias et al. also found that CD38 expression is upregulated in aged macrophages via exposure of these cells to senescence-associated secretory proteins (SASP), especially the cytokines interleukin-6 (IL-6), IL-10, and tumor necrosis factor-α (TNF-α). This suggests that the inflamming process induces NAD+ salvage in macrophages to promote a pro-inflammatory
phenotype, thereby perpetuating chronic low-grade inflammation during aging.

4. **Targeting immunometabolism**

The evidence presented above implicates alterations in immunometabolism in promoting age-associated inflammation. A natural question which emerges from this is whether reprogramming immunometabolism during aging can ameliorate or reverse aging-dependent inflammatory conditions. A recent paper by Minhas and colleagues in *Nature* [36] sheds some light on this. Here, the authors noted an age-associated increase in prostaglandin E2 (PGE$_2$) synthesis in macrophages, and demonstrated using Seahorse assays that PGE$_2$ suppressed both glycolysis and mitochondrial oxygen consumption in human monocyte-derived macrophages through signaling via the EP2 receptor. During aging, macrophages polarized to a pro-inflammatory phenotype, had defects in phagocytic capacity, and interestingly upregulated intracellular glycogen synthesis and storage. Most importantly, inhibiting EP2 in brain microglia decrease pro-inflammatory activation and restored spatial memory in aged mice, and peripheral blockade of this receptor also suppressed hippocampal inflammation and restored performance on memory tasks in aged mice. These findings underscore the utility of targeting immunometabolic reprogramming as a therapeutic intervention to reverse age-associated inflammatory diseases and disorders.

More generally, targeting mitochondrial metabolism is a promising strategy for reversing generalized chronic inflammatory activation in macrophages and monocytes, including in the aging context. Anti-inflammatory M2-like macrophages have long been known to depend on oxidative metabolism for energy production [37]. Some evidence suggests that activation-related defects in OXPHOS underly the inability of pro-inflammatory M1-like macrophages to repolarize to an M2-like phenotype upon IL-4 stimulation [38]. The key studies cited in the sections above [24,32,34–36] indicate that aging causes mitochondrial dysfunction in both monocytes and macrophages, and therefore inflamming may be related to an inability of these cells to polarize to anti-inflammatory phenotypes. This suggests that therapies which target mitochondrial function have the potential to be efficacious in treating inflamming and reducing age-related chronic diseases.

In addition to NAD precursors discussed above, another promising example of this strategy is spermidine supplementation, which has been shown to have anti-aging effects attributed to promoting mitochondrial function [39]. Spermidine promotes hypusination of the eukaryotic translation initiation factor 5A (eIF5A), which is reduced during aging and linked to immunosenescence [40]. eIF5A hypusination is also central to M2-like macrophage polarization and promotes oxidative metabolism of these anti-inflammatory cells [41]. As such, this is another example of a potential pathway by which immunometabolic reprogramming may be used to target inflamming and immunosenescence.

5. **Future perspectives**

The papers featured in this review are some of the first to demonstrate that aging induces metabolic reprogramming in monocytes and macrophages that is associated with inflamming and age-related disease. There are however still tremendous opportunities to move the field forward, as a number of important research questions remain. For example, aging is the single greatest risk factor for many diseases [1], and it remains to be seen if reprogramming metabolism in aged immune cells
can ameliorate symptoms of these diseases. Immunometabolic reprogramming has been implicated in the pathogenesis of a variety of aging-associated diseases, including COVID-19 [4,42,43], atherosclerosis [44], and cancer [45,46], and it is plausible that aging drives increased incidence of these diseases through alterations in immunometabolism.

Additionally, the evidence presented above implicates immunometabolic reprogramming in polarizing macrophages toward pro-inflammatory phenotypes. This may be true for monocytes as well, as aging increases proportions of intermediate and non-classical monocytes in circulation [23,47]. Indeed, research suggests that non-classical monocytes have some degree of mitochondrial dysfunction [48], but there are not yet conclusive links between aging, immunometabolism, and monocyte phenotype. Preventing monocyte differentiation to macrophages in vitro remains a significant challenge in easily studying monocyte phenotypic dynamics, but modern in vivo methods of studying this may shed new light on this problem. For example, recent studies have used whole body stable isotope-labeled substrate administration to study metabolic reprogramming of immune cells in an in vivo context [49]. Similar methods may be useful to profile, for example, glucose or NAD metabolism in aging immune cells in a more physiologically-relevant manner. Enhanced in vivo methods may also increase the feasibility of human clinical/translational studies in immunometabolism, as most research in the field to date has been limited to in vitro or rodent studies.

Notably, recent advances in single cell technologies also have the potential to revolutionize the field of immunometabolism [50]. These techniques could permit interrogation of metabolic and phenotypic variation of monocytes and macrophages even in rare tissue resident populations, which have historically been difficult to isolate in sufficient numbers to study using standard bulk in vitro methods. Single cell RNA sequencing has been widely used to study the diversity of immune cell phenotypes, including in aging [51]. Recently, computational approaches to identify metabolic reprogramming in single cell RNA sequencing data have been described [52]. Likewise, a method for extracellular flux analysis using flow cytometry has been published [53], which permits Seahorse-like data collection on individual cells. Single cell metabolomics approaches have also been recently developed using imaging mass spectrometry [54]. Coupled with rapid isolation techniques, these strategies could permit studying immunometabolism in a context more relevant to that seen in vivo.

Another area of potential interest is the impact of aging on intermediate metabolite levels in myeloid cells. While several recent studies have examined NAD+ metabolism, less is known about the regulation of immunomodulatory metabolites such as succinate, citrate, fumarate, itaconate, etc. by aging. Lactate has also recently been shown to be immunosuppressive by promoting lactylation of histones [55] and is a byproduct of glycolysis, and thus may play a role in immunosenescence. In addition to metabolites, soluble proteins upregulated by the aging process are also potential mediators of metabolic reprogramming. For example, growth differentiation factor-15 has recently been shown to be highly differentially expressed in aging [56], and this protein is known to alter macrophage metabolism [57] and is correlated with monocyte dysfunction during aging [58]. A variety of other proteins, especially those which are major SASP constituents, are likely to modulate immunometabolism and may be principal players in inflammaging and/or immunosenescence.

6. Conclusions

The past few years have seen several major advances in our knowledge of innate
immunometabolism and aging, as outlined above. It now appears that aging promotes mitochondrial dysfunction and metabolic reprogramming of monocytes and macrophages toward pro-inflammatory phenotypes, and that shifts in NAD+ metabolism from de novo synthesis to the salvage pathway likely play a central role in this. Likewise, targeting immunometabolism appears to be a promising strategy to treat aging-associated diseases and disorders. While the featured papers have laid the groundwork in this field, much is still to be done. Particularly, future studies using in vivo methods and translationally-relevant models will be key to further advances in this field. A fuller understanding of aging impacts on immunometabolism could lead to development of targeted therapeutics for a variety of age-related diseases.

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**Conflict of interest**

The author declares no conflict of interest in this paper.

**References**

1. Niccoli T, Partridge L (2012) Ageing as a risk factor for disease. *Curr Biol* 22: R741–R752.
2. Franceschi C, Garagnani P, Parini P, et al. (2018) Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol* 14: 576–590.
3. Williamson EJ, Walker AJ, Bhaskaran K, et al. (2020) Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 584: 430–436.
4. Pence BD (2020) Severe COVID-19 and aging: are monocytes the key? *GeroScience* 42: 1051–1061.
5. Viboud C, Boëlle P, Cauchemez S, et al. (2004) Risk factors of influenza transmission in households. *Br J Gen Pract* 54: 684–689.
6. Hernandez-Vargas EA, Wilk E, Canini L, et al. (2014) Effects of aging on influenza virus infection dynamics. *J Virol* 88: 4123–4131.
7. Falsey AR, Walsh EE (2000) Respiratory syncytial virus infection in adults. *Clin Microbiol Rev* 13: 371–384.
8. Franceschi C, Capri M, Monti D, et al. (2007) Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev* 128: 92–105.
9. Nikolich-Žugich J (2018) The twilight of immunity: Emerging concepts in aging of the immune system review-article. *Nat Immunol* 19: 10–19.
10. O’Neill LAJ, Kishton RJ, Rathmell J (2016) A guide to immunometabolism for immunologists. *Nat Rev Immunol* 16: 553–565.
11. Mills EL, Kelly B, Logan A, et al. (2016) Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages. *Cell* 167: 457–470.e13.
12. Tannahill GM, Curtis AM, Adamik J, et al. (2013) Succinate is an inflammatory signal that induces IL-1β through HIF-1α. *Nature* 496: 238–242.
13. Arts RJW, Novakovic B, Horst RT, et al. (2016) Glutaminolysis and fumarate accumulation integrate immunometabolic and epigenetic programs in trained immunity. *Cell Metab* 24: 807–819.
14. Lampropoulou V, Sergushichev A, Bambouskova M, et al. (2016) Itaconate links inhibition of succinate dehydrogenase with macrophage metabolic remodeling and regulation of inflammation. *Cell Metab* 24: 158–166.
15. Domínguez-Andrés J, Novakovic B, Li Y, et al. (2019) The itaconate pathway is a central regulatory node linking innate immune tolerance and trained immunity. *Cell Metab* 29: 211–220.e5.
16. Yarbro JR, Emmons RS, Pence BD (2020) Macrophage immunometabolism and inflamming: roles of mitochondrial dysfunction, cellular senescence, CD38, and NAD. *Immunometabolism* 2: e200026.
17. Zasłona Z, O’Neill LAJ (2020) Cytokine-like roles for metabolites in immunity. *Mol Cell* 78: 814–823.
18. Makowski L, Chaib M, Rathmell JC (2020) Immunometabolism: from basic mechanisms to translation. *Immunol Rev* 295: 5–14.
19. Wang A, Luan HH, Medzhitov R (2019) An evolutionary perspective on immunometabolism. *Science* 363: eaaar3932.
20. Lee KA, Robbins PD, Camell CD (2021) Intersection of immunometabolism and immunosenescence during aging. *Curr Opin Pharmacol* 57: 107–116.
21. Murphy MP, O’Neill LAJ (2018) Krebs cycle reimagined: the emerging roles of succinate and itaconate as signal transducers. *Cell* 174: 780–784.
22. López-Otín C, Blasco MA, Partridge L, et al. (2013) The hallmarks of aging. *Cell* 153: 1194–1217.
23. Pence BD, Yarbro JR (2018) Aging impairs mitochondrial respiratory capacity in classical monocytes. *Exp Gerontol* 108: 112–117.
24. Saare M, Tserel L, Haljasmägi L, et al. (2020) Monocytes present age-related changes in phospholipid concentration and decreased energy metabolism. *Aging Cell* 19: e13127.
25. Gon Y, Hashimoto S, Hayashi S, et al. (1996) Lower serum concentrations of cytokines in elderly patients with pneumonia and the impaired production of cytokines by peripheral blood monocytes in the elderly. *Clin Exp Immunol* 106: 120–126.
26. McLachlan JA, Serkin CD, Morrey KM, et al. (1995) Antitumoral properties of aged human monocytes. *J Immunol* 154: 832–843.
27. Pence BD, Yarbro JR (2019) Classical monocytes maintain ex vivo glycolytic metabolism and early but not later inflammatory responses in older adults. *Immun Ageing* 16: 3.
28. Renshaw M, Rockwell J, Engleman C, et al. (2002) Cutting edge: impaired toll-like receptor expression and function in aging. *J Immunol* 169: 4697–4701.
29. Sinclair L V, Barthelemy C, Cantrell DA (2020) Single cell glucose uptake assays: a cautionary tale. *Immunometabolism* 2: e200029.
30. Reinfeld BI, Madden MZ, Wolf MM, et al. (2021) Cell-programmed nutrient partitioning in the tumour microenvironment. *Nature* 593: 282–288.
31. Yoshino J, Baur JA, Imai S (2018) NAD+ intermediates: the biology and therapeutic potential of NMN and NR. Cell Metab 27: 513–528.
32. Cameron AM, Castoldi A, Sanin DE, et al. (2019) Inflammatory macrophage dependence on NAD+ salvage is a consequence of reactive oxygen species-mediated DNA damage. Nat Immunol 20: 420–432.
33. Verdin E (2015) NAD+ in aging, metabolism, and neurodegeneration. Science 350: 1208–1213.
34. Minhas PS, Liu L, Moon PK, et al. (2019) Macrophage de novo NAD+ synthesis specifies immune function in aging and inflammation. Nat Immunol 20: 50–63.
35. Covarrubias AJ, Kale A, Perrone R, et al. (2020) Senescent cells promote tissue NAD+ decline during ageing via the activation of CD38+ macrophages. Nat Metab 2: 1265–1283.
36. Minhas PS, Latif-Hernandez A, McReynolds MR, et al. (2021) Restoring metabolism of myeloid cells reverses cognitive decline in ageing. Nature 590: 122–128.
37. Vats D, Mukundan L, Odegaard JJ, et al. (2006) Oxidative metabolism and PGC-1beta attenuate macrophage-mediated inflammation. Cell Metab 4: 13–24.
38. Van den Bossche J, Baardman J, Otto NA, et al. (2016) Mitochondrial dysfunction prevents repolarization of inflammatory macrophages. Cell Rep 17: 684–696.
39. Liang Y, Piao C, Beuschel CB, et al. (2021) eIF5A hypusination, boosted by dietary spermidine, protects from premature brain aging and mitochondrial dysfunction. Cell Rep 35: 108941.
40. Zhang H, Alsaleh G, Feltham J, et al. (2019) Polyamines control eIF5A hypusination, TFEB translation, and autophagy to reverse B cell senescence. Mol Cell 76: 110–125.e9.
41. Puleston DJ, Buck MD, Klein Geltink RI, et al. (2019) Polyamines and eIF5A hypusination modulate mitochondrial respiration and macrophage activation. Cell Metab 30: 352–363.e8.
42. Pence BD (2021) Aging and monocyte immunometabolism in COVID-19. Aging 13: 9154–9155.
43. Codo AC, Davanzo GG, de Brito Monteiro L, et al. (2020) Elevated glucose levels favor SARS-CoV-2 infection and monocyte response through a HIF-1alpha/glycolysis-dependent axis. Cell Metab 3: 437–446.e5.
44. Ketelhuth DFJ, Lutgens E, Bäck M, et al. (2019) Immunometabolism and atherosclerosis: perspectives and clinical significance: a position paper from the Working Group on Atherosclerosis and Vascular Biology of the European Society of Cardiology. Cardiovasc Res 115: 1385–1392.
45. Roy DG, Kaymak I, Williams KS, et al. (2020) Immunometabolism in the tumor microenvironment. Annu Rev Cancer Biol 5: 137–159.
46. O'Sullivan D, Sanin DE, Pearce EJ, et al. (2019) Metabolic interventions in the immune response to cancer. Nat Rev Immunol 19: 324–335.
47. Hearps AC, Martin GE, Angelovich TA, et al. (2012) Aging is associated with chronic innate immune activation and dysregulation of monocyte phenotype and function. Aging Cell 11: 867–875.
48. Ong SM, Hadadi E, Dang T, et al. (2018) The pro-inflammatory phenotype of the human non-classical monocyte subset is attributed to senescence. Cell Death Dis 9: 266.
49. Ma EH, Verway MJ, Johnson RM, et al. (2019) Metabolic profiling using stable isotope tracing reveals distinct patterns of glucose utilization by physiologically activated CD8+ T cells. Immunity 51: 856–870.e5.
50. Artyomov MN, Van den Bossche J (2020) Immunometabolism in the single-cell era. *Cell Metab* 32: 710–725.
51. Tabula Muris Consortium (2020) A single-cell transcriptomic atlas characterizes ageing tissues in the mouse. *Nature* 583: 590–595.
52. Wagner A, Wang C, Fessler J, et al. (2021) Metabolic modeling of single Th17 cells reveals regulators of autoimmunity. *Cell* 184: 4168–4185.
53. Argüello RJ, Combes AJ, Char R, et al. (2020) SCENITH: A flow cytometry-based method to functionally profile energy metabolism with single-cell resolution. *Cell Metab* 32: 1063–1075.e7.
54. Rappez L, Stadler M, Triana S, et al. (2021) SpaceM reveals metabolic states of single cells. *Nat Methods* 18: 799–805.
55. Zhang D, Tang Z, Huang H, et al. (2019) Metabolic regulation of gene expression by histone lactylation. *Nature* 574: 575–580.
56. Tanaka T, Biancotto A, Moaddel R, et al. (2018) Plasma proteomic signature of age in healthy humans. *Aging Cell* 17: e12799.
57. Ackermann K, Bonaterra GA, Kinscherf R, et al. (2019) Growth differentiation factor-15 regulates oxLDL-induced lipid homeostasis and autophagy in human macrophages. *Atherosclerosis* 281: 128–136.
58. Pence BD, Yarbro JR, Emmons RS (2021) Growth differentiation factor-15 is associated with age-related monocyte dysfunction. *Aging Med* 4: 47–52.

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