CORRESPONDENCE

Centenarian longevity is positively correlated with IgE levels but negatively correlated with C3/C4 levels, abdominal obesity and metabolic syndrome

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Centenarians have delayed or absent onset and interaction of age-related disturbances and might be a prototype of human longevity and successful aging.[1] What are the factors and models of centenarian longevity? This issue has confused humans for thousands of years. Studies comparing centenarians and other oldest-old individuals could identify the factors related to centenarian longevity, and analysis of their relationships in these oldest-old individuals could improve the models of centenarian longevity.[1] All these factors and models could be used to identify therapeutic targets for the prevention of age-related disturbances and the promotion of centenarian longevity.

Metabolic syndrome represents metabolic disturbance in the human body and has an increasing prevalence of 20–25% worldwide.[2] An increasing prevalence of metabolic syndrome with age has been reported in up to 42.0% of elderly individuals in the United States.[3] However, it remains unclear whether the prevalence of metabolic syndrome is further elevated in centenarians from China. The immune system is closely related to metabolic syndrome, which is therefore considered a chronic immune-related disease.[4] However, controversial conclusions have been documented, and the relationships between metabolic syndrome and immune function need to be clarified by large-scale studies in different populations, including the oldest-old population.[5] Moreover, assessing whether immunological markers and metabolic syndrome are the factors related to centenarian longevity and whether their relationships exist in the oldest-old population as a model of centenarian longevity are greatly needed and important.

Hainan is a longevity region with the highest population density of centenarians in China. The China Hainan Centenarian Cohort Study, which has a large sample size, was performed to investigate the relationship network between immunological markers, metabolic syndrome, abdominal obesity, and centenarian longevity in the oldest-old population. From July 2014 to October 2017, 1297 individuals in the 18 cities and counties of Hainan Province participated in the study and completed all tests (Table S1), including 655 centenarians with an age ≥100 years and 642 other oldest-old individuals <100 years. All participants were identified by the National Civil Registry provided by the Hainan Civil Affairs Bureau.

All the oldest-old individuals had a median age of 100 (84–102) years, ranging from 80 to 116 years. The percentages of males, individuals with metabolic syndrome and individuals with abdominal obesity were 30.3% (393 participants), 18.7% (242 participants), and 31.9% (414 participants), respectively. Based on the logistic regression analysis (Table S2), there were significantly lower prevalence rates of metabolic syndrome and abdominal obesity in the centenarians ($P < 0.05$ for all). Moreover, centenarians showed significantly associations with higher immunoglobulin E (IgE), IgG and kappa levels; lower IgM and complement component 3 (C3) and 4 (C4) levels; and lower levels of anti-Jo-1 and anti-pm-scl antibodies ($P < 0.05$ for all). As shown in Table S3, metabolic syndrome and abdominal obesity were significantly associated with lower IgE levels and higher C3 and C4 levels ($P < 0.05$ for all). Figure 1 shows the relationship network between immunological markers, abdominal obesity, metabolic syndrome, and centenarian longevity in the oldest-old population.

IgE is a significant indicator of the immune system.[3] The balance in immune function and metabolic status might play an important role in centenarian longevity, whereas immune dysfunction might be connected to the development of metabolic syndrome and abdominal obesity. The current study found that IgE had a negative relationship with metabolic syndrome and a positive relationship with centenarian longevity in the oldest-old Chinese population. Insulin resistance has been shown to inhibit allergic response and IgE in previous basic research. IgE intervenes in the activation of endothelial and mast cells and influences the secretion and action of cell-related cytokines.[6] These cells and cytokines have the potential to participate in the development of abdominal obesity and metabolic syndrome, and IgE might correlate with metabolic syndrome by directly or indirectly interacting with these cells and cytokines.[7]

The complement system is critical for innate and adaptive immunological mechanisms and plays a part in life processes and centenarian longevity. C3 and C4 are the main proteins of the complement pathways, play prominent roles in the complement system, and have been identified as early markers of metabolic syndrome in previous studies. The current study confirmed that C3 and C4 had positive relationships with metabolic syndrome and negative relationships with centenarian longevity in the oldest-old Chinese population. C3 and C4 are synthesized in the liver. The cytokines that interfere with hepatic synthesis are mainly secreted by excessive adipose tissue.[8] Moreover, C3 and C4 are synthesized

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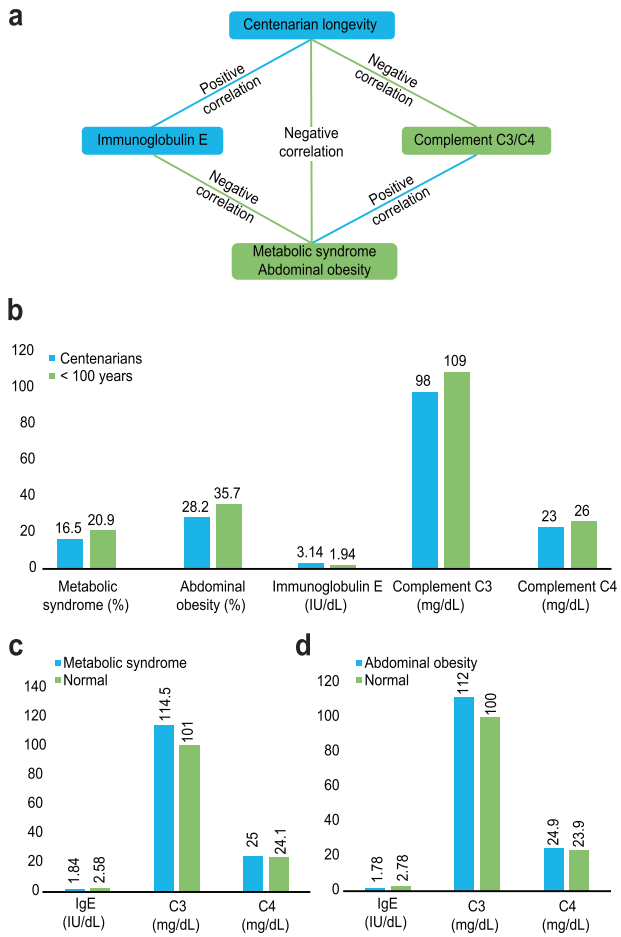

Fig. 1 Relationship network and data basis. **a** Relationship network between immunological markers, metabolic syndrome, abdominal obesity, and centenarian longevity in the oldest-old population. **b** Prevalence rates of metabolic syndrome and abdominal obesity and immunoglobulin E (IgE) and complement component 3 (C3) and 4 (C4) levels in centenarians and other oldest-old individuals (<100 years). **c** IgE, C3, and C4 levels of centenarians with and without metabolic syndrome. **d** IgE, C3, and C4 levels of centenarians with and without abdominal obesity

by activated adipocytes and macrophages and act as both cytokines and adipokines. These cytokines might influence insulin receptor–substrate interactions and aggravate insulin resistance. As the major degraded product and active fragment of C3, acylation stimulating protein (ASP, C3a-desArg) has insulin-like properties and promotes lipid synthesis in adipocytes. Therefore, ASP resistance might lead to an increase in ASP precursor levels, similar to the increase in insulin levels resulting from insulin resistance.

Abdominal obesity has been considered to be the most significant manifestation of metabolic syndrome associated with insulin resistance and metabolic syndrome.[8] The current study determined that abdominal obesity and metabolic syndrome not only had negative relationships with centenarian longevity but also had negative relationships with IgE and positive relationships with C3 and C4 in the oldest-old Chinese population. Abdominal adipose tissue might lead to insulin resistance and act as an immune organ.[9] Adipose tissue might produce different complement factors and trigger an immune response.[9] Elevated expression of C3 and C4 is related to visceral adipose and abdominal obesity.[6] ASP (C3a-desArg) could promote lipogenesis in adipose cells. Therefore, C3 might increase abdominal obesity and influence lipid metabolism, further causing metabolic syndrome and interfering with centenarian longevity.[10]

Based on the findings from the current study, an immune system with the qualities of increased IgE and reduced C3 and C4 might prevent metabolic syndrome and abdominal obesity and promote centenarian longevity, all of which should be considered therapeutic targets in the prevention of metabolic syndrome and in the promotion of centenarian longevity. Moreover, centenarian longevity had positive relationships with other immunoglobulins, such as IgG and kappa, and negative relationships with autoantibodies, such as anti-Jo-1 and anti-pm-scl antibodies. These immune indices might also participate in the development of centenarian longevity and successful aging.

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AUTHOR CONTRIBUTIONS

S.F., Y.L., F.Z., F.X.L., F.Q.L., J.D., Y.Z., and Y.Y. contributed to the study design, performed the data collection and analyses, and drafted the paper.

ADDITIONAL INFORMATION

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