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Cardiovascular Disease Delay in Centenarian Offspring: Role of Heat Shock Proteins

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Abstract

Cardiovascular disease is a major cause of morbidity and mortality of older Americans. We have demonstrated recently that centenarian offspring, when compared with age-matched controls, avoid and/or delay cardiovascular disease and cardiovascular risk factors. Given recent evidence suggesting that higher circulating levels of HSP70 predict the future development of cardiovascular disease in established hypertensives and a recent study demonstrating a decrease in HSP60 and HSP70 with advancing age, we hypothesized that HSP70 levels would be lower in centenarian offspring compared with controls. The circulating serum concentration of HSP70 in 20 centenarian offspring and 9 spousal controls was analyzed using a modified HSP70 ELISA method. Centenarian offspring showed approximately 10-fold lower levels of circulating serum HSP70 compared with spousal controls ($P < .001$). The exact biological significance of the extremely low levels of circulating serum HSP70 observed in centenarian offspring thus far is not clear. However, circulating HSP has been shown to correlate in diseases or disorders in which there is destruction or damage to target tissues or organs, including cardiovascular diseases and numerous autoimmune disorders. We hypothesize that low levels of circulating serum HSP70 may be an indicator of a healthy state and point to longevity of the host; therefore, our results suggest that levels of circulating serum HSP70 may be a marker for longevity.

Keywords

aging; cardiovascular disease; chaperokine; centenarian; heat shock proteins; longevity

INTRODUCTION

Longevity Runs in Families

Prior research suggests that longevity runs in families. Both the parents and the siblings of centenarians[1] have been shown to have significantly longer life expectancies than the average for their birth cohorts. More recently, we have demonstrated that the children of centenarians, who are typically in their 70s and 80s, have a survival advantage when compared with age-matched controls whose parents died at an average life expectancy. Furthermore, these individuals demonstrate a reduced relative prevalence[2] as well as a delay in the age of onset for heart disease, hypertension, and diabetes.[3] Interestingly, no differences have been found

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between the offspring of centenarians and controls for several other age-related diseases such as cancer, osteoporosis, and dementia.[2] This suggests that it is perhaps the avoidance or delay of cardiovascular disease and cardiovascular risk factors that facilitate the survival to exceptional old age.

Heat Shock Protein and Its Role in Cardiovascular Disease and Longevity

Heat shock proteins (HSPs) are highly conserved proteins found in all prokaryotes and eukaryotes. The primary role of HSPs is to chaperone, transport, and fold proteins when cells are exposed to a variety of stresses.[4] Under normal physiological conditions, HSP is expressed at low levels; however, a wide variety of stressful stimuli including environmental, pathological, or physiological stimuli can induce a marked increase in intracellular HSP synthesis[4] known as the stress response.

It is now clear that HSP can also exit mammalian cells,[5] interact with cells of the immune system, and exert immunoregulatory effects.[6] The ability of HSP to act as cytokine and chaperone is termed the chaperokine activity of HSP.[7]

The expression of HSP in the early stages of cardiovascular disease might result from one or a combination of factors. For example, risk factors for atherosclerosis such as hyperlipidemia, diabetes, smoking, and hypertension cause oxidative stress. Oxidative stress, in turn, may lead to the induction of HSP expression in vascular smooth muscle cells.[8] In addition, prior research indicates that circulating HSP70 levels predict the development of cardiovascular disease in subjects with established hypertension.[9,10] These authors suggest that HSP70 protects against or modifies the progression of atherosclerosis in this subject group.

With the avoidance and/or delay of cardiovascular disease in centenarian offspring, the evidence suggesting a protective role of HSP70 for cardiovascular disease and a recent study demonstrating an apparent decrease in HSP60 and HSP70 with advancing age,[11] we hypothesized that levels of HSP70 would be lower in centenarian offspring when compared with age-matched controls.

METHODS

The criteria for eligibility, recruitment, and main study outcomes have been published elsewhere.[2]

Enzyme-Linked Immunosorbent Assay

Serum from 20 centenarian offspring and 9 spousal controls was analyzed for the concentration of HSP70 using the HSP70 enzyme-linked immunosorbent assay (ELISA) kit (StressGen Biotechnologies, Victoria, BC, Canada) as previously described.[11] The total cell protein content within the serum was determined by Bradford analysis using bovine serum albumin as a standard.

Univariate statistical analysis was done using the Student's *t* test.

RESULTS

A complete accounting for all potential participants for both groups and a complete description of all enrolled participants have been published elsewhere.[2]

HSP70 levels were measured in convenience subsample of 20 centenarian offspring and nine controls using an HSP70 ELISA kit (StressGen). We demonstrate that circulating HSP70 in

centenarian offspring serum (Fig. 1; unfilled bars) is approximately 10 times less than circulating HSP70 found in the serum of spousal controls (Fig. 1; filled bars; $P < .001$).

DISCUSSION

Our prior work has demonstrated that the offspring of centenarians are healthier than age-matched controls.[2] In particular, the delay and/or avoidance of cardiovascular disease may be key for their potential survival to exceptional old age.

The physiological role of circulating heat shock proteins has yet to be defined. However, our results are in agreement with others who have shown that there is a progressive decline in serum Hsp60 and Hsp70 levels with aging.[11] The exact biological significance of the extremely low levels of circulating HSPVO observed in centenarian offspring is not clear. In general, circulating HSP have been shown to correlate in diseases or disorders in which there is destruction or damage to target tissues or organs, including cardiovascular diseases and numerous autoimmune disorders. Low levels of circulating HSP may be an indicator of a healthy state and point to longevity of the host; therefore, we suggest that levels of circulating HSPVO may be a marker for longevity.

Ultimately, further study of circulating HSPVO needs to be performed in a larger sample of individuals to better understand this phenomenon and to account for some of the confounders such as current health status and health habits using multivariate analyses.

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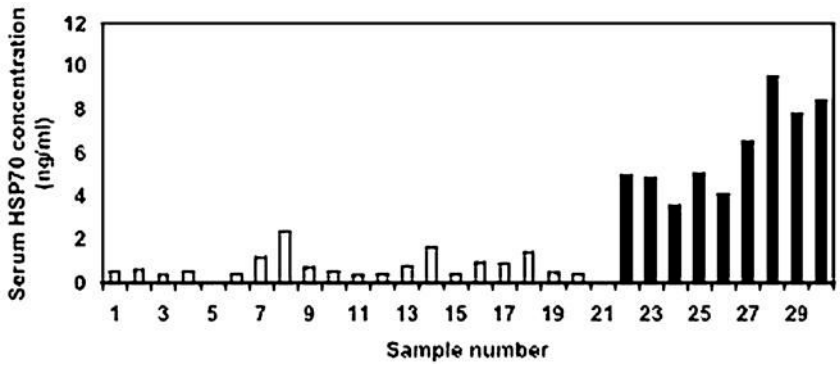

FIGURE 1.

Concentration of circulating HSP70. Sera from 20 centenarian offspring (*unfilled bars;* 1–20) and nine spousal controls (*filled bars;* 22–30) were analyzed for the concentration of HSP70 using the HSP70 ELISA kit (StressGen Biotechnologies). Data represent the serum HSP70 concentration and represent two experiments performed with similar results ($P < .001$).