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【学会報告】

第6回国際ローマ映画祭プログラム「イタリアと日本：高齢者に優しい2つの国」

田中　雅嗣
東京都健康長寿医療センター研究所
老化制御研究チーム・健康長寿ゲノム探索

夏のある朝、イタリア・ボローニャ大学のClaudio Francheschi教授から電話がかかってきた。国際ローマ映画祭で黒澤明監督生誕100年を記念して日本特集を行う。「イタリアと日本：高齢者に優しい2つの国」と題してプログラムを組むので、講演を依頼したいとのことであった。Francheschi教授は、実験病理学が専門で、高齢者の免疫系の研究を行っている。ヨーロッパ連合の予算を獲得してGenomics for Healthy Aging (GEHA) projectを組織している（http://www.geha.unibo.it)。GEHAコンソーシアムにはヨーロッパの11カ国の25研究室と中国が参加している。GEHA研究では5300組の高齢同胞と2650人の若年対照群を集めており、ヒトを対象とした長寿研究として最大規模である。私は2004年にGEHA projectが開始された頃から、2回ボローニャ大学を訪問し、ミトコンドリアDNA解析について討議した。今回も国際ローマ映画祭の後に、ボローニャ大学で「ミトコンドリア・デイ」と題したシンポジウムが開催され、イタリアのミトコンドリア研究者と交流することができた。

「イタリアと日本：高齢者に優しい2つの国」では、最初にイタリアの映画評論家が日本とイタリアの映画から、高齢者の登場するシーンを抽出して、解説した。日本映画で取り上げられたのは小津安二郎監督の「東京物語」であった。笠知衆の扮する義父が、戦争で夫を亡くした嫁（原節子）に再婚を勧めるシーンであった。この映画は、年老いた両親の一世一代の東京旅行を通じて、家族の絆、夫婦と子供、老いと死、人間の一生、それらを冷徹な視線で描いた作品である（Wikipedia)。他の映画のシーンが上映された後に、Francheschi教授と私が、長寿を達成するためにどんなことができるかをイタリア語と英語でそれぞれ討論し、同時通訳を介して聴衆との質疑応答を行った。以下に掲げる英文は、サブプログラムのパンフレット用に用意した短文である。

その要点をここに記す。ES細胞やiPS細胞ではミトコンドリアゲノムの遺伝子発現が抑制されている。ミトコンドリアからのROS産生が上昇すると、細胞分化が誘導され、分化万能性が失われる。私の仮説は、組織幹細胞において加齢と共にミトコンドリアからのROS産生が上昇し、それによって自己複製能が失われ、免疫系・神経系・運動器系の臓器・組織の予備能が低下し、これが個体老化をもたらすというものである。

なぜ女性と男性の間で10%の寿命差があるかを考える。東京都健康長寿医療センターの新井冨生病理診断部長の総説（マイクロキメリズム　－女性の体内に存在するY染色体について考える－病理と臨床2010年11月号）によると、男児を出産した経験のある女性の臓器や癌組織にY染色体が検出されるという。胎児と母親は胎盤を介して細胞の交流がある。これをmaternal microchimerism（母系マイクロキメリズム）と呼ぶ。Y染色体は男児に由来することが明確であるので定量的分析が可能であるが、女児を妊娠している間にもマイクロキメリズムが生じている。マイクロキメリズムはSLEや慢性関節リウマチなどの自己免疫疾患の頻度が女性において高いことを説明する。また、白血病などの造血器腫瘍の治療の一環として骨髄幹細胞移植を実施する場合に、母親と子供の移植において組織適合性白血球抗原（HLA）の一致度が多少低くても、拒絶反応が起こりにくい。この現象もマイクロキメリズムによって母親と子供の間で免疫学的寛容が成立しているためと説明されている。

一方、長寿の女性を調べると40歳ないし45歳以上で出産経験をもつ人が多いという疫学研究結果がある。私が考えた仮説は、母親が胎児から新鮮な幹細胞の供給を30歳ないし40歳に受けると、寿命が延長するというものである。成人になっても骨髄幹細胞は末梢血中に流れている。出産時に胎盤から採取される臍帯血には造血幹細胞が多量に含まれている。男性の組織幹細胞の寿命が90歳で尽きるのに対して、女性は妊娠時に胎児から供給された幹細胞のブースター効果によって100歳まで生存できる。ネットを調べてみると、自らの長寿や若返りを目指して妊娠し、胎児から幹細胞の供給を受けた後に、中絶してしまうという恐ろしい可能性も指摘されていた。

男性は、妊娠することが今のところ不可能であるので、自分の組織幹細胞を痛めつけないように喫煙や禁酒など節制に務めなくてはならない。ローマでの講演の終わりに、草食男子やイクメンなど、若い日本人男性の傾向を紹介してお茶を濁した。他に「夫の寿命は妻の寿命に依存するので、奥さんを大切にすべきだ」など、いくつかの論点も英文で記したので、ご一読いただければ、幸いである。

Longevity in Japan: Why number one for women and number five for men?

Masashi Tanaka
Department of Longevity and Health
Tokyo Metropolitan Institute of Gerontology

In this talk, I will introduce the results of our genetic analysis of the mitochondrial genome of Japanese centenarians. I will also present my personal view on the possible avenues for attaining longevity, focusing especially on lifespan extension of Japanese men. I have to apologize for my biased opinions, because I am a male researcher mainly studying the mitochondrial genome variations that are transmitted through the maternal line.

Mitochondria

Mitochondria are the intracellular power plants providing almost all of the energy necessary for cellular activity. Mitochondria are furnaces combusting hydrogen extracted from nutrients with oxygen taken up by respiration. Mitochondria are the major sites producing reactive oxygen species, which molecules can attack proteins, lipids, and DNA. Thus, we can speculate that mitochondria are tightly linked with the ageing process.

Mitochondrial genome

The mitochondrial genome is a small circular DNA of 16,569 base pairs compared with the human nuclear genome of 3 giga base pairs. Each mitochondrion carries several copies of mitochondrial DNA. The amount of messenger RNA transcribed from the mitochondrial genome is about one-third of the total RNA of cells. This genome is highly polymorphic among individuals, because the evolutionary rate of mtDNA is 10-20 times higher than that of the nuclear DNA. We can hypothesize that functional differences in the mitochondrial genome among human individuals contribute to their susceptibility to various age-related metabolic diseases, such as type 2 diabetes and metabolic syndrome.

Longevity-associated mitochondrial haplogroups

In 1998, we reported that Japanese centenarians are enriched in mitochondrial haplogroup D and that this haplogroup confers resistance to various age-related diseases. In 1999, Prof. Franceschi's group at the University of Bologna reported haplogroup J to be associated with longevity in Italian centenarians. Recently we demonstrated that subhaplogroup D4a is abundant in Japanese semi-supercentenarians (age over 105 years). Haplogroup D is characterized by an amino acid replacement (leucine 237 to methionine in ND2) in complex I of the respiratory chain; whereas subhaplogroup D4a is represented by an amino acid replacement (isoleucine 78 to threonine in Cytb) in complex III of the respiratory chain. These polymorphisms are supposed to be linked with the antioxidant effect or stabilization of the mitochondrial enzymes. Both haplogroup D and subhaplogroup D4a are specific to Asians, whereas haplogroup J is specific to Europeans. Thus different targets should be selected for prediction of longevity in Japan and Italy.

How to live long?

If you are male, my answer is: Marry a Japanese lady! The average lifespan of Japanese women is 86.44 years, which is the longest among all of the countries in the world. Widowers live fewer years than men who live together with their wives. So one could say that wives are life-savers for their husbands. Men's lifespan is dependent on the longevity of their wives. For women to live with aged husbands may be too stressful, and women can enjoy the single lifestyle after their husbands have passed away. Thus, 'grief care' would be more important for widowers than for widows. In contrast, widows live longer than women who live together with their husbands. The average lifespan of Japanese men is 79.59 years, which is only the 5th place among the world's countries. If you are female, to marry a Japanese gentlemen can be a good choice for a long life!

Box 1. Lifespan of women and men in the world's top countries

Female		Male	
Japan	86.44	Qatar	81.0
Hong Kong	86.1	Hong Kong	79.8
France	84.5	Iceland	79.7
		Switzerland	79.7
		Japan	79.59

Female-male lifespan difference

In many countries, the average lifespan of men is about 90% of that of women. Although this fact has been mainly attributed to biological differences between men and women, sociological fac-

tors also contribute to the lifespan differences between men and women. The lifespan of women is close to that of men in the Middle-East and South Asian countries, where the status of women in society should be improved. The lifespan of men is far below that of women in the previous communist countries, where suicide rates of men are high because of drastic negative changes in the economy. To prolong the lifespan of Japanese men, we should re-activate the Japanese economy and create support systems for depressed citizens, especially the men.

Characteristics of Japanese centenarians

The percentage of disabled centenarians is higher for females than for males. This fact is interpreted to mean that many female centenarians are survivors of cerebrovascular diseases, myocardial infarction, or other diseases; whereas males do not generally survive these disorders. This phenomenon is consistent with the psychological profiles of centenarians. Japanese male centenarians are nervous about their health and frequently visit clinics for health checkups. For both females and males, Japanese centenarians are less corporative (independent or going their own way). For one's longevity, it may be a wise personal policy to ascribe psychological stresses not to oneself but to others.

Longevity of women and importance of type of cuisine

Menstruation is associated with the monthly loss of iron from the body. Free iron in the cells is a source of reactive oxygen species, which attack cellular components, such as lipids, proteins and DNA. Furthermore, estrogen (female hormone) is believed to protect women against oxidative stress. These facts may contribute to the greater longevity of the female.

Most Japanese cuisine utilizes various kinds of soybean products, such as 'miso' (soy paste), 'shoyu' (soy source), and 'natto' (fermented soybeans), which contain soybean isoflavones having antioxidant and estrogen-like effects. Also, both Japanese and Italian cuisines are characterized by the frequent use of seafood, which contain polyunsaturated fatty acids. Furthermore, by decreasing salt intake and preventing hypertension, we have successfully suppressed the incidence of death from cerebral hemorrhage. I believe that we Japanese should further increase the intake of fruits and vegetables as in the case of the Mediterranean people.

Microchimerism and tissue stem cells

It has been reported that women who give birth after 40 years of age live longer than women who do not. This longevity effect is, at least in part, explained by genetic factors, including mitochondrial genome polymorphisms, because the brothers of those long-lived women live longer than other men. In connection with this observation, I am now interested in microchimerism. Mothers and fetuses exchange each others cells. We can detect the cells from fetuses in the body of mothers, although the number of such cells is small. For one's longevity, it is important to maintain stem cells that are continuously providing somatic cells in each tissue. The tissue stem cells donated from the fetus may contribute to the longevity of the mother. Unfortunately, it is impossible for men to enjoy this possible benefit from the fetus, so we should find another way for the male to get a boost from stem cells.

How can we promote healthy longevity of Japanese men?

Traditionally Japanese men have been supposed to devote themselves to their work. Japanese baby boomers have to learn a new style of life from the newer generations. After retirement from their job, many Japanese company-first men, who had enjoyed a high position in the hierarchy within companies, find it difficult to join their local communities. Especially for men, to maintain active interaction with local societies in later life is a prerequisite for longevity. Thus we should introduce some type of re-education system to convert company-first men to community-connected men.

Herbivore men vs. carnivore women

I am not so pessimistic, because new types of Japanese men are emerging. In 2005 the Japanese author Maki Fukasawa coined the expression 'so-shoku danshi' vs. 'niku-shoku joshi', which literally means 'herbivore men' vs. 'carnivore women.' 'Herbivore men' are interested in their fashion and uninterested in earning or spending much money. Another type is 'iku-men' (nursing men), who are males actively involved in the care of children. Both 'herbivore men' and 'iku-men' seem to refuse to be too masculine. These new types of Japanese men may be expected to enjoy greater longevity in the future.

Conclusions

Japan is an aging aged country. Although both biology and genetics are important to understand the mechanism of longevity, we should also keep a keen eye on the various sociological and psychological aspects of aging. I believe that stimulation of our lives by close interaction with our partners is a key facet for longevity.