RESEARCH SUMMARY

The fetal programming of telomere biology hypothesis: an update
Entringer, S., de Punder, K., Buss, C. and Wadhwa, P.D. (2018)
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When our cells divide, their DNA must replicate too so that each 'daughter' cell contains the same DNA as the original one. This process is remarkably precise, but still not completely so. In each division, a very small quantity of the DNA at the tip of each chromosome cannot be replicated, so each daughter chromosome is very slightly shorter than the original one. The only reason why important genetic information is not lost between one cell generation and the next is because the DNA at the ends of chromosomes is different from the rest. These 'end regions' of DNA, which are called telomeres, are repetitive and contain no genes, so no crucial information disappears when they shorten. That is, until they reach a critical length, when the cell loses function and dies. Telomere loss has been linked to normal ageing and to the onset of common diseases of old age. Both the original telomere length and the rate at which they degrade differs between individuals, and there is some scientific evidence to suggest that those with long or slowly-degrading telomeres are likely to live longer and have some protection against these diseases.

The telomere system, which also includes telomerase, an enzyme that re-attaches telomere DNA to chromosome ends, is well developed by the time that a baby is born. Many parameters that set babies' future health prospects and disease risk are thought to be established in the womb, in a process known as 'foetal programming'. In this paper, Sonja Entringer and co-workers from Charité-Universitätsmedizin Berlin, Germany and the University of California School of Medicine, Irvine, CA, USA suggest that the telomere system is susceptible to foetal programming and, therefore, that a sub-optimal environment in the womb will increase the chance that the baby is born with short or fast-shrinking telomeres. This child will therefore have an increased risk of ageing-related diseases at the other end of his or her life. Furthermore, they suggest that maternal stress will influence this programming through a range of biochemical pathways, so the children of a severely stressed mother can start life already at a greater risk of diseases that will only arise in future decades.

Entringer and her colleagues begin their overview by expanding on the concept of foetal programming. Any individual's risk of developing a disease arises from a combination of his or her innate susceptibility (e.g. derived from genetic factors) with environmental risks (such as poor diet, stress or smoking). Two individuals with the same variants of given disease susceptibility genes may end up with very different risks as a result of environmental factors that affect how those genes are expressed, and this effect is particularly strong very early in life, in infancy and before birth. They further suggest that the telomere system is strongly affected by this, providing a direct, biochemical link between foetal development and much later cellular ageing.

The telomere-telomerase system is a dynamic one, in which telomerase expression and activity determines how many division cycles a cell can go through before it becomes ‘senescent’. In adults, most cell types divide rarely and therefore have little telomerase activity. The presence of some telomerase, however, is necessary to preserve healthy cell function, and cells with defective telomerase are defective also in (for instance) energy production and the DNA damage response.

Most studies of the human telomere system across the lifespan have concentrated only on telomere shortening. Entringer and her colleagues suggest that it is necessary to consider this process alongside measures of telomerase activity; furthermore, they propose that the ‘maximal telomerase activity capacity’ (mTAC) of white blood cells is a measurable parameter that can reflect stable differences in the telomere system between individuals.

Shortened telomeres and low telomerase activity have both been associated with several mainly age-related diseases, including cardiovascular disease, diabetes, depression and other psychiatric disorders. Interestingly, too, the prognosis of some transplant patients appears to be more closely linked to telomere length in the donor than in the recipient. This implies, at least, that the differences in prognosis might be directly caused by the differences in the telomere system, but this has not been proven and further studies are needed.

Many researchers have proposed a link between physical or social disadvantage and a suboptimal telomere system, and some have suggested that this arises, at least in part, from enhanced stress. Exposure to severe stress or trauma has also been linked to changes in the telomere system, and there have been suggestions that behaviour changes that alleviate stress might have a beneficial effect on the system, slowing down cellular ageing.

Entringer and her colleagues then set out several biological processes that might act together to pass the effects of stress or the unhealthy lifestyle choices that often accompany it into the telomere system. These include oxidative stress; inflammation; metabolic processes, particularly those stimulated by the intake of fats; and the activity of the HPA axis or ‘stress axis’. This is the name given to three linked glands that are activated in stressful situations, leading to increased production of the hormone cortisol. High and poorly regulated activity of this axis, leading to raised cortisol levels, has been linked to shorter telomeres and lower telomerase expression. Exposure to cortisol has been shown to inhibit telomerase production in some types of white blood cell, which divide rapidly and therefore need telomerase to maintain healthy chromosomes.

The length of an individual’s telomeres is related to their initial length at birth; their attrition rate, which is affected by stress; and the number of divisions that their cells have been through. The authors describe experiments in humans and other animals that suggest that that initial ‘set point’ at birth is crucial for determining health and disease risk in later life. They summarise studies in mammals and birds that suggest, together, that the telomere length at birth and the initial attrition length are better

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predictors of lifespan than the length or attrition rate in later life. These effects appear to persist even when the animals concerned are exposed to infection.

Similarly, telomere length has been tracked and compared over time in groups of human subjects, showing that most differences in telomere dynamics and the consequent risk of age-related diseases are set at birth or in babyhood. These studies and others imply that the length of telomeres at birth is the principal factor that determines their length later in life, which highlights the importance of researching telomere biology in babies and young children. Telomere shortening can be expected to affect health and ageing more severely in individuals in whom the 'set point' of telomere length at birth had been shorter.

There are several possible explanations for the observation that healthy lifestyles in adults are associated with healthy telomere activity. The most obvious is perhaps that telomere dynamics is one of the biological mechanisms through which such behaviour improves general health. However, it may be that individuals with longer telomeres are, through some unknown mechanism, predisposed to healthy behaviour, or it may be that both the telomeres and the behaviour are influenced by a third variable: and early-life adversity is a very likely candidate.

This adds weight to the theory that the development or 'programming' of telomeres before birth is key to how an individual will age. Certainly, telomerase is very active in the embryo and foetus, particularly in the early months of pregnancy. Typically, telomeres grow rapidly in the embryo, change little between the late foetal and newborn stages, and then shrink more rapidly in early childhood than at any other stage of life. This suggests that the telomere system responds most readily to environmental factors between conception and early childhood.

Entringer and her co-authors then suggest that the child's crucial 'set point' of telomere biology is determined by environmental as well as genetic factors, and that exposing a baby to extreme or inappropriate stress either before or after birth can, through the telomeres, affect that individual's health in the decades to come. The same biological processes that affect telomere shortening in adults, including inflammation and the stress response, are likely to have an even greater effect on the sensitive telomeres of the foetus in the womb.

Studies in both animals and humans have shown an association between stress in pregnancy and shortened telomeres in the offspring. Furthermore, those in humans showed an association between adverse conditions during pregnancy and suboptimal telomere development in the offspring that is likely to be mediated through the maternal stress response. This effect can sometimes be observed after many decades; individuals who had experienced famine during the siege of Leningrad before or soon after birth were found to have shorter telomeres than their peers after 70 years. Other studies have shown similar effects after severe psychosocial stress in pregnancy.

The mechanism that the authors propose through which maternal stress influences foetal telomere biology is itself a biological one, arising through pathways that connect

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the mother to the foetus through the placenta. Many published studies have implicated these pathways in determining various aspects of foetal health. Relatively few of these, however, concern the telomeres. One study in rodents has shown that protein restriction in the womb led to both biochemical stress and accelerated telomere shortening in the pups, and another that treating mother rats with antioxidants during pregnancy could reduce cellular ageing in the offspring. Women who suffered from some diseases during pregnancy, including diabetes and hypertension, have been found to give birth to infants with shortened telomeres.

The telomere system can be controlled by epigenetic modifications, which are changes to DNA chemistry that are not passed on genetically. These are known to be affected by stress, and the authors suggest that the ways in which early-life epigenetic changes might affect telomere biology deserve further study. It is likely, however, that this and other ways through which the chemical environment influences a growing embryo start at the very earliest point in pregnancy, with the cytoplasm of the fertilised egg. Thus, the health of a woman before her pregnancy begins will affect the way the embryo develops. Women under physical and psychological stress often fail to conceive and can find pregnancy difficult when they do so.

It is at least plausible that women who have had particularly difficult lives pass on their problems through direct and indirect chemical effects on many of their childrens' systems, including their telomeres. Furthermore, the telomeres of babies and young children are more sensitive to stress than those of adults, so adversity in early life will also affect cellular ageing. This implies, however, that the effect of prenatal adversity can be at least partly compensated for after birth by, for example, secure attachment and sensitive parenting.

Entringer and her co-authors conclude this extensive review by suggesting some avenues for further research. There is much we don't yet know about how the conditions that a baby encounters before and after birth influence the 'set point' of his or her telomeres. Longitudinal studies tracking individuals over decades will be useful, but most studies of the effects of stress on telomere biochemistry and cell biology will only be possible in animal models. But it is likely that the roots of many common diseases of middle and old age lie in pregnancy and infancy, and that supporting the parents of young infants and encouraging nurturing care should improve the health and wellbeing of those infants throughout their lives.

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