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Two studies: Covid-19 and childhood obesity THE CAUSAL ROLE OF TELOMERES ON METABOLISM

LORRAINE UNIVERSITY OF EXCELLENCE

68 laboratories

4 486 researchers
and professors

1947 PhD
students

108 scientific
platforms and
equipment

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The objectives of the GEENAGE research project, supported by the Lorraine University of Excellence, are the comprehension and prevention of normal and pathological aging. It focuses on the late repercussions of early events such as in-utero exposure to certain metabolic deficiencies, the existence of cardiovascular risk factors or chronic inflammatory diseases.

By studying the genetic and epigenetic factors that can influence cardiovascular and metabolic diseases, the GEENAGE project has focused in particular on **telomeres**, structures that protect the ends of chromosomes, to better understand their role in the health and aging. **The whole question is whether their length is just an indicator of biological age or a real determinant of the aging trajectories.**

The presence of short telomeres is indeed associated with an increased prevalence of degenerative diseases related to aging. The mechanistic links of this association are the subject of several basic and clinical research studies. The answer to this question is of major importance for the definition of preventive and therapeutic strategies for pathological aging.

Studies confirming the hypothesis of the causal role of telomere length

On the 30th of June, during the Lorraine Université d'Excellence webinar, Professor Athanase Benetos, professor of geriatric medicine and biology of aging at the University Hospital of Nancy, and Doctor Simon Toupance, associate professor in cellular and molecular biology at the University of Lorraine, discussed two studies of their group which confirmed the role of telomeres in the predisposition of certain pathologies and in their severity:

- The link between telomere length and lymphocyte count in older subjects hospitalized with Covid-19

In mid-2020, 38 people, aged 65 to 104, were admitted to the geriatrics department of the Nancy CHRU: 17 patients were hospitalized for Covid-19, the other 20 for various reasons.

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Blood samples were taken from all of these patients to record lymphocyte counts after a complete blood count test. The length and distribution of their telomeres were measured¹ to then be correlated with the number of lymphocytes in Covid-19 patients and non-Covid-19 patients. These correlations were finally compared between these two groups of patients.

Lymphocyte counts were lower in COVID-19 patients than in non-COVID-19 patients, and lymphocyte counts were inversely correlated with the proportion of shorter telomeres. A drop in the number of T cells is the main cause of lymphopenia in coronavirus disease 2019, the extent of which is an indicator of the severity of COVID-19.

The results demonstrated that people infected with SARSCoV-2 and having short telomeres show a delay in their immune response, which leads to a deficit in their blood pool of T cells. They also suggest that COVID-19 exposes the telomere length-dependent limited replicative reserves of T cells in the elderly with short telomeres.

Data from other research groups on children with COVID-19 confirm this correlation. Children who are otherwise healthy usually have a mild clinical course when infected with SARS-CoV-2. While lymphopenia is a major prognostic feature of COVID-19 in adults, it is a minor aspect of low prognostic value in children with COVID-19. Since the average length of telomeres in children is greater than in adults, their replicative capacity to rapidly accelerate the production of T cells even compensates for a drastic loss of these T cells due to SARS-CoV-2 infection.

This means that the older adults have a considerable replicative disadvantage compared to younger adults, which could contribute to older adults' propensity for severe COVID-19 lymphopenia. That said, from birth, telomere length is highly variable from one individual to another, since heritability is estimated at around 70% for telomere length and around 30% for telomere shortening depending on age. This high variability of telomere length observed in adult population could potentially explain the propensity for severe COVID-19 lymphopenia in younger adults with short telomeres.

Although conducted on a small cohort of older people of European ancestry, all surviving the disease for at least 15 days, this study provided the optimal setting to examine the link between telomere

¹ The result of a collaboration between clinicians, biologists and mathematicians, as part of the GEENAGE project, the method makes it possible to measure short telomeres proportions and to know the distribution of telomere length. This is a major advance that demonstrates that if telomeres shorten with age, their distribution shape remains the same.

The IMPACT GEENAGE project is a structuring research project that is part of the IMPACT program of the Lorraine University of Excellence (LUE) initiative.

The GEENAGE project is a multidisciplinary initiative of excellence which aims to produce new strategies for the diagnosis and management of normal and pathological aging, and to draw an emerging trajectory for health research at the University of Lorraine in the 10 coming years, both nationally and internationally.

The project wishes to identify signatures that will be characteristic and, if possible, predictive of a pathology or the general aging process. With the contribution of digital sciences, these pathological "signatures" could become tools for precision medicine, the prevention of age-related frailty, morbidity and loss of autonomy.

This initiative of excellence associates biologists, engineers, psychologists and doctors and makes the link between pre-existing structuring operations in the field of health research, in particular the FHUs CARTAGE (Cardiac and ARterial AGEing) and ARRIMAGE (Digestive and OsteoARticular Remodeling-Inflammation-Immunomodulation-Metabolism in diseased AGEing), and RHU FIGHT-HF (FIGHTing Heart Failure).

length and lymphopenia in this disease.

Longitudinal association of telomere dynamics with obesity and metabolic disorders in young children

Obesity and metabolic disorders in young children represent one of the most important public health problems in the world. Shorter telomeres are already present in obese children. This could be explained either by the potential effect of obesity on the shortening of telomeres in a critical period of growth and proliferative activity or by the causal role of pre-existing short telomeres on obesity and the development of metabolic disorders.

Recruited between 2014 and 2015 by the Group of Pr. Charmandari of the Medical School of Athens, 73 Greek children aged 2 to 10 suffering from overweight and obesity were monitored until 2019².

All clinical examinations, hematological, biochemical and endocrinological investigations were carried out in the laboratory of Pr. Charmandari under identical conditions. All the children and their parents were informed about the complications of obesity and the need for the whole family to adopt a healthier lifestyle. The Nancy team performed several telomeric analyses in these children from leucocytes drawn at inclusion and during the follow-up. All these measurements were carried out in Nancy in the Telomere laboratory of the Inserm Unit DCAC.

In this longitudinal study of young children telomere length shortening was not accelerated during the follow-up period in obese subjects. However, short telomeres at inclusion were associated with higher metabolic disorders during the follow-up. These results indicate that short telomeres precede the development of childhood obesity and suggest that telomeres may be involved in the development of this pathology and metabolic disorders very early in life, which has a major impact on health.

If these results are confirmed by larger cohorts, telomere length could be considered a risk factor for early obesity and therefore be used to propose personalized interventions for children at risk.

² In collaboration with the Kapodistrian University of Athens Medical School and "Aghia Sophia" Children's Hospital in Athens.

LORRAINE UNIVERSITY OF EXCELLENCE brings together eight partners around a research and training program responding to the major economic and societal challenges of the 21st century. Confirmed to I-SITE status in 2021, the strength of its innovation strategy lies in the ability to mobilize its interdisciplinary, systemic and entrepreneurial approach to issues, such as: new materials, energy, ecological and digital transition, societal transition, and health.

To learn more: <https://www.univ-lorraine.fr/lue/espace-presse>

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