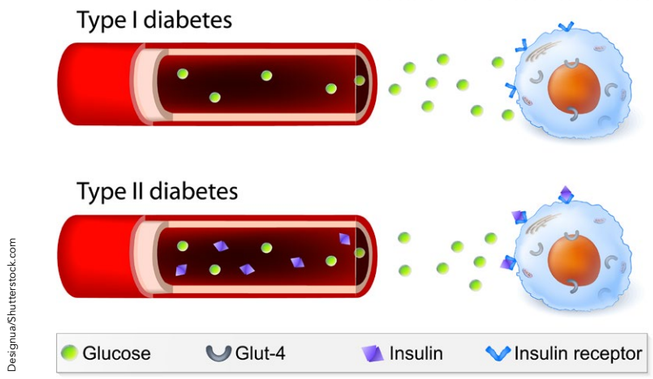
Diabetes and early life *IGF1* gene methylation

In utero early-life epigenetic changes may predispose individuals to develop adulthood diseases such as diabetes which is globally highly prevalent. Prenatal nutrition impacts epigenetic changes such as DNA methylation leading to long lasting effects. Dr Masato Kantake and colleagues at Juntendo University Nerima Hospital, Tokyo, Japan, study insulin-like growth factor 1 (IGF1) gene methylation in preterm infants with low nutrition condition. Their findings may help nutritional management in preterm infants as well as providing a link with adult diseases such as diabetes.

Diabetes mellitus type 1 and type 2 (T1DM and T2DM) are both chronic diseases marked by high blood sugar due to insulin deficiencies. In T1DM, pancreatic cells no longer produce insulin whereas in T2DM, the ability of cells and tissues to respond to insulin is diminished (insulin insensitivity) or there is reduced levels of insulin secretion. Worldwide, an estimated 316 million individuals have diabetes, 90% of whom have T2DM. Patients may present with changes in body weight, hunger, thirst, frequent urination, and fatigue. There is a complex interplay between both genetic and environmental risk factors in the development of T2DM, with lifestyle factors such as being overweight, lack of exercise, and age, associated with T2DM development. Gene mutations (changes to DNA sequences) and epigenetics (inherited genetic traits resulting from alterations in chromatin structure in chromosomes without any change in DNA sequences) have a key role in T2DM pathogenesis.



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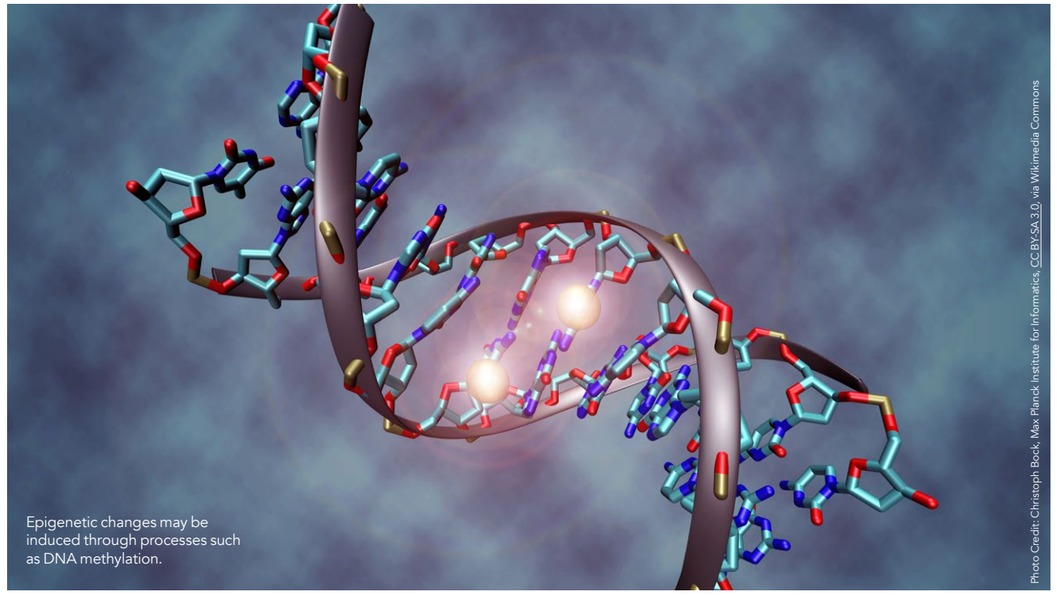
Epigenetic changes may be induced through processes such as DNA methylation, histone modifications, chromosomal remodelling, and regulation of noncoding RNA, and are influenced by external and internal factors. DNA methylation is the modification of a DNA base by enzymes while histone modifications to histone proteins occurs via processes such as methylation, acetylation, or phosphorylation. In diabetes, histone modification, specifically histone methylation, impacts the pancreatic cells which secrete insulin and affects insulin secretion and sensitivity. Epigenetic changes are thought to be inherited and therefore passed through generations. Insulin-like growth factor 1 (IGF1), encoded by the *IGF1* gene, is a growth hormone protein important for childhood growth and regulation of blood glucose in adults.

Developmental Origins of Health and Disease (DOHAD) is the research into how early life (prenatal and perinatal) conditions predispose individuals to developing disease. The DOHAD hypothesis is that during adverse conditions, a foetus can adapt to ensure its survival. Early-life gene epigenetic changes can affect our development and determine characteristics in adulthood. The intrauterine environment and events (programming) can influence and shape the development of diseases in later life with nutrition, environmental and lifestyle



Epigenetic changes may be induced through processes such as DNA methylation.

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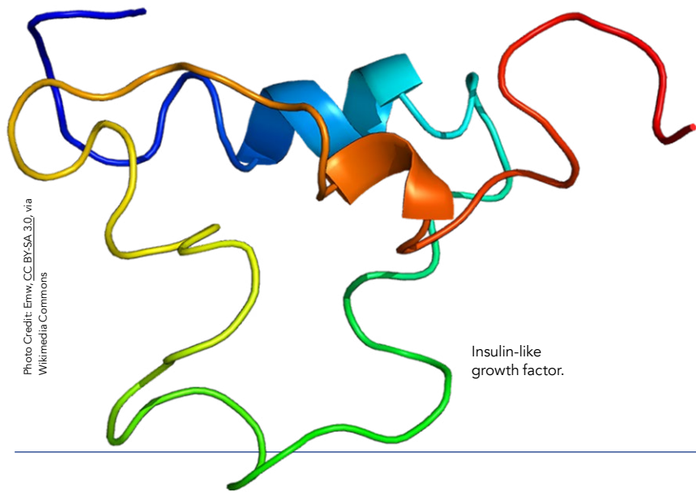
factors influencing DNA methylation, in particular maternal diet. Research carried out by Dr Masato Kantake and colleagues at Juntendo University Nerima Hospital, Tokyo, focuses on such epigenetics. The team are specifically interested in the central effects of *IGF1* gene methylation and when this methylation or epigenetic programming occurs during gestation. Their research helps to understand development of adult diseases such as diabetes and may aid in the nutritional management of preterm infants.

HEIGHT, T2DM DEVELOPMENT, AND *IGF1* GENE METHYLATION

IGF1 is not just important during foetal development; it is required for childhood growth and in adulthood. Low levels of IGF1 are associated with diabetes, cardiovascular disease, and lipid metabolism abnormalities. A systematic review by other researchers on diabetes and height reveal an inverse relationship between height of adults and T2DM indicating that shorter individuals have a higher risk of T2DM development. This is an indirect risk, and the finding may be explained by various confounding factors. One explanation could be related to foetal development and IGF1 secretion. A study published in 2014 using extracted DNA from blood in adults reveals increased *IGF1* gene methylation levels accompanied by reduced IGF1 serum levels in diabetes compared to controls. The same study suggested such increased DNA methylation levels may stop gene transcription and consequently production of IGF1, explaining the low serum levels noted. Low IGF1 secretion is associated with shorter height and risk of adult T2DM while high IGF1 levels promotes growth and is associated with reduced T2DM risk. As *IGF1* methylation affects IGF1 secretion, changes to this methylation may drive these mechanisms.

>32 weeks gestation is a critical period for IGF1 gene methylation, subsequent body growth, and predisposition to diabetes.



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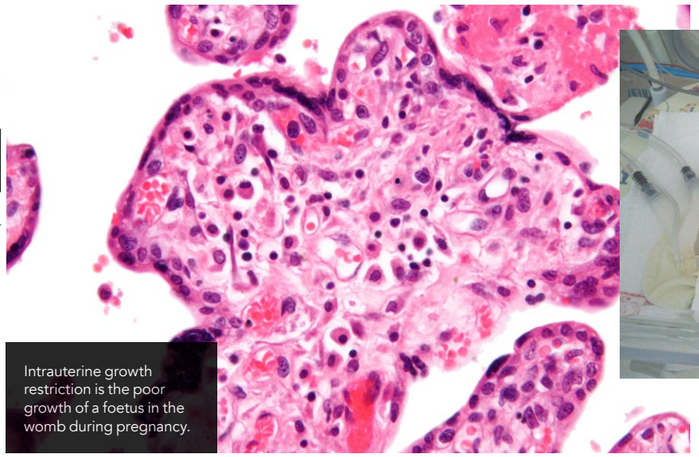
Insulin-like growth factor.

EARLY LIFE *IGF1* GENE METHYLATION

Studies by other researchers in full-term infants have shown that high methylation of the *IGF1* gene and low serum IGF1 levels are associated with infant height. Furthermore, it is known that full-term infants with intrauterine growth restriction (IUGR) – reduced or poor growth of a foetus in utero caused by a variety of conditions including low nutrition – are



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Intrauterine growth restriction is the poor growth of a foetus in the womb during pregnancy.

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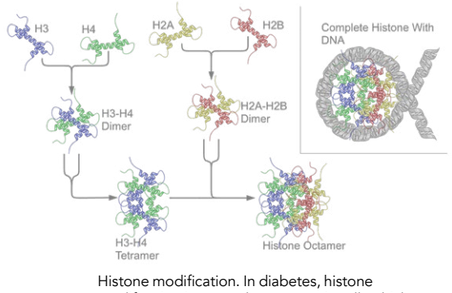
32+ weeks gestation is a critical period for *IGF1* gene methylation, subsequent body growth, and predisposition to diabetes.

at higher risk for T2DM. This is related to high rates of *IGF1* gene DNA methylation and subsequent low IGF1 levels. Kantake's research in preterm infants aimed to determine when during the intrauterine development activation of the *IGF1* gene methylation programme occurs and if this is a response to maternal signals in the postembryonic stage or before. The researchers examined DNA in blood of preterm infants born less than 32 weeks gestation and included infants with and without IUGR. They found reduced methylation levels in the *IGF1* gene promoter 2 region during adverse intrauterine conditions (eg, low nutrition) in preterm infants with IUGR. This appears to be an adaptation to intrauterine conditions such as malnutrition and the team hypothesise that *IGF1* gene methylation may be kept low to maintain IGF1 levels, an adaptation by the foetus to ensure growth and survival. Full-term IUGR infants have high *IGF1* gene DNA methylation and low IGF1 secretion and Kantake's study reveals preterm IUGR infants have low methylation and higher IGF1 secretion; this suggests that >32 weeks gestation is a critical period for *IGF1* gene methylation, subsequent body growth, and predisposition to diabetes.

This research provides vital insight into this epigenetic programming in early life, the importance of nutrition, and adult disease onset.



Histone modification. In diabetes, histone modification impacts the pancreatic cells which secrete insulin, affecting insulin secretion and sensitivity.

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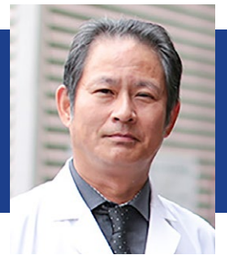
Kantake suggests that after 32 weeks gestation or postnatally, the *IGF1* methylation could be reset or reprogrammed as shown to occur with glucocorticoid receptor gene. He argues that evaluation of this methylation status either in utero >32 weeks or after birth could help in the management of these infants. Kantake explains, 'longitudinal studies are currently underway to further understand the environmental factors that affect *IGF1* DNA methylation postnatally and whether good nutritional management in these infants may induce *IGF1* gene DNA methylation reprogramming'. His findings, that the third trimester (specifically >32 weeks) are critical for DNA methylation, may provide a useful model to understand and predict adult diseases such as T2DM, marked by high DNA methylation and low IGF1 secretion.

EPIGENETIC TREATMENT TARGETS AND PREVENTION OF DISEASE

Modifications to histone proteins via methylation, acetylation, or phosphorylation are catalysed by enzymes. Changes to such processes, especially methylation, can cause altered gene expression with several such genes identified in T2DM pathogenesis. It is hoped that targeting catalytic enzymes such as histone methyltransferase with inhibitor drugs may reverse the erroneous epigenetic changes and restore normal gene expression in T2DM. Histone deacetylase inhibitor also can have a therapeutic activity for several epigenetic diseases. Such treatment candidates are under investigation, many in pre-clinical animal studies. Epigenetic changes could serve as indicators of susceptibility to disease or as biomarkers in early disease detection, flagging at risk individuals to lifestyle interventions.

Kantake's study suggests that knowledge of *IGF1* gene methylation status could help to prevent and treat T2DM and more research is needed to explore this further. This research provides vital insight into this epigenetic programming in early life, the importance of nutrition and adult disease onset.



Behind the Research

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Research Objectives

Masato Kantake's research provides vital insight into epigenetic programming in early life, the importance of nutrition, and adult disease onset.

Detail

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Bio
Masato Kantake completed his PhD at the age of 31 years, at Chiba University. He is Director of the Neonatal Medical Center of Juntendo University Nerima Hospital. He is Senior Associate Professor of Pediatrics, Juntendo University. Kantake is one of the pioneers in epigenetics research during the neonatal period.

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Collaborators
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Personal Response

Your research provides valuable information as to when IGF1 gene methylation occurs, and you suggest it has implications as a model for adult disease onset and in nutritional management of preterm infants. What are your future research plans to gain further understanding of these implications?

"We are developing an IUGR model rat to elucidate the pathology. This will allow us to glean important knowledge about the critical window for *IGF1* gene methylation and possibility for prevention and treatment of diseases which are mediated by low IGF1 secretion.

In parallel with the basic research plan, we are planning two clinical research studies. One is a longitudinal observational study of infants born before 34 weeks of gestation. The other is an intervention trial regulating intestinal microbiota which affects epigenetic modification. Breastfeeding and/or supplementation of bifidobacteria may have a beneficial effect for preterm infants through *IGF1* gene methylation."

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