Early Growth and Ageing


Epidemiological studies have revealed a relationship between poor early growth and the development of cardiovascular disease, type 2 diabetes, insulin resistance and other features of the metabolic syndrome. The mechanistic basis of this relationship is not known. However, compelling evidence suggests that early environmental factors such as nutrition play an important role. Studies of individuals in utero during a period of famine have shown a direct relationship between maternal nutrition and glucose tolerance. Further evidence has come from studies of monozygotic twins who were discordant for type 2 diabetes. These have revealed that when there was discordance for type 2 diabetes, the diabetic twin had a lower birthweight than the non-diabetic co-twin. Nutrition during the early postnatal period has also been shown to have long-term consequences on metabolic health. Excess nutrition and accelerated growth during the neonatal period has been suggested to be particularly detrimental. In contrast, slow growth during lactation appears to be protective against future metabolic disease. A number of animal models, including that of maternal protein restriction, maternal calorie restriction and maternal iron restriction, have been developed to elucidate mechanisms linking the early environment and future disease susceptibility. The maternal protein restriction model has been one of the most extensively characterized. In this model rodents are fed a low (8%) protein diet during pregnancy and/or lactation. This maternal dietary manipulation leads to a low birthweight and development of many features of the metabolic syndrome including type 2 diabetes in the offspring. Glucose intolerance is associated with β-cell dysfunction and insulin resistance. Insulin resistance is accompanied by changes in expression of key components of the insulin-signaling cascade in muscle and adipocytes. We have demonstrated similar changes in tissue biopsies from young men with a low birth weight. More recent studies with the maternal protein restriction model have revealed that nutrition and growth during fetal and early postnatal life can influence longevity. Offspring born to low protein-
fed dams have a low birthweight but when suckled by control dams undergo rapid postnatal growth. These ‘recuperated’ offspring gain excess weight when weaned onto standard laboratory chow and are more susceptible to diet-induced obesity and have a reduced longevity. This reduced longevity is associated with evidence of increased cellular ageing including accelerated telomere shortening, increased oxidative damage and expression of markers of cell senescence. In contrast offspring of control dams that are suckled by low protein-fed dams grow slowly during lactation, gain less weight when weaned onto standard laboratory chow and are resistant to diet-induced obesity and have an increased longevity. This increase in longevity was associated with reduced telomere shortening, increased expression of antioxidant enzymes and increased expression of SIRT1, an NAD-dependent histone deacetylase that has been implicated in mediating the effects of calorie restriction to increase longevity.