

Effects of diet-induced obesity on mammary development, function and plasticity

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Obesity is now recognised as an independent risk factor in several life-threatening diseases including diabetes, hypertension and cardio-vascular disease. More recently it has been proposed to have adverse effects on mammary tumorigenesis. Indeed a recent meta-analysis of the available epidemiological data proposed that 25% of the risk of developing breast cancer could be attributed to obesity and an effect of obesity on mammary gland function is not entirely surprising considering the intimate relationship which exists between adipose and mammary tissues. In order to begin to address the relative importance of obesity on both metabolic and developmental aspects of mammary function, we have developed a diet-induced mouse model based on a simplified “cafeteria-style” high fat diet. Animals provided with a high fat diet ate approximately 40% more calories and gained weight at three times the rate of controls. They exhibited reduced conception rates, increased peripartum pup mortality and impaired lactogenesis. The impairment of lactogenesis involved lipid accumulation in the secretory epithelial cells indicative of an absence of copious milk secretion. Although there were clear reproductive and metabolic defects, development of the mammary gland was also affected. We thus undertook a series of studies in which animals were kept on high fat diets for up to 1 year or which underwent weight gain/loss cycles during this period. Our results demonstrate that obesity markedly decreases branching morphogenesis and alveolar differentiation. Furthermore we demonstrate that a high fat diet, in the absence of obesity creates a different phenotype involving dramatic increases in ductal diameters. Finally, we have demonstrated that these changes are at least partially reversible if obese animals are placed onto a low fat diet. Although these results do not provide evidence for increased breast cancer risk, the changes are entirely consistent with such a possibility and we thus believe that studies relating to mammary tumour development in this model are warranted.