Complex Impact of Obesity on Type 2 Diabetes

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Obesity, the result of excess body fat, is now well recognized as a major health problem. In fact, the American Heart Association recently classified obesity as a major risk factor for coronary heart disease [1]. It is firmly established that obesity, mainly central obesity, plays a dominant role in reducing the efficacy of insulin action in peripheral tissues, leading to insulin resistance and its consequences [2]. Type 2 diabetes, metabolic syndrome, hypertension and atherosclerosis are among the clinical syndromes that result from increases in insulin resistance [3]. In many populations, the increasing prevalence of obesity is paralleled by an increase in diabetes prevalence that is reaching epidemic proportions [4]. The study by Abdul-Ghani et al. in this issue of IMAJ [5] demonstrates that the Arab population in Israel is no exception. Arab women, because of their higher rate of obesity, had a higher prevalence of diabetes than men in the same community. It is worth noting that whereas Western countries showed no gender preference for either obesity or type 2 diabetes, women in all Arab populations studied to date were at greater risk than men to develop both obesity and diabetes [6–10]. This high frequency of obesity among Arab women is more likely to reflect lifestyle than genetic background, since among Arab high-schoolers the male and female children had similar rates of obesity [11] that were not statistically different from the rate among Jewish children [12].

It is now well established that the development of type 2 diabetes results from an interaction between the subject's genetic makeup and his/her environment. Lifestyle and obesity are among the principal environmental factors that enhance the risk of developing diabetes. Men and women of the same ethnic group and living in the same community are likely to have a similar genetic makeup. Thus, gender differences in diabetes prevalence observed by Abdul-Ghani and his team are likely to be entirely attributed to obesity. Since this important risk factor is potentially preventable [13] this observation has critical clinical significance. It means that subjecting women in this community to a primary prevention program could prevent at least a quarter of these cases of diabetes. Given the high risk of diabetes in the Arab population [14], as well as the impact diabetes has on morbidity, mortality and healthcare expenditures, implementing such a program in this community would be highly cost-effective.

Diabetes has very significant morbidity and mortality. In addition to tripling the risk for coronary heart disease [15], it increases the risk for damage to the eyes, kidney and nerves. It was found that 30%–40% of diabetic subjects will have microvascular complications during the course of their disease [16]. Moreover, the duration of diabetes is among the principal risk factors for microvascular complications [17]. The present report by Abdul-Ghani et al. adds another important dimension to the impact of obesity on diabetes: they found that obese women not only had a higher frequency of diabetes, but those who develop diabetes do so at a younger age [5]. Thus, obesity has multiple roles in diabetes: it is an important risk factor for having the disease, and it is also the main determinant of the age of disease onset. This second role of obesity is probably the reason for the recent surge of type 2 diabetes observed among children and young adults [18]. As a result, obese subjects will have diabetes for longer and will be at higher risk for developing microvascular complications. Furthermore, obese diabetic patients are more likely to have metabolic syndrome than non-obese subjects. Diabetic subjects with metabolic syndrome have an almost twofold increase in their risk for coronary heart disease as compared to diabetic patients without metabolic syndrome [19].

Clearly, obesity significantly worsens the prognosis of diabetic subjects. By fighting obesity we will not only reduce the incidence of diabetes, but will also have "healthier" diabetic patients. Those who are destined to have diabetes due to their genetic makeup will be at lower risk for having both micro- and macrovascular complications.

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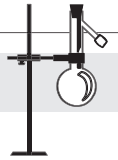

The mechanism of formation of extrachromosomal circular DNA in Drosophila

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Background: Genomic instability is a hallmark of tumor cells. One of its intriguing aspects is the formation of extrachromosomal circular DNA (eccDNA). eccDNA contains sequences derived primarily from genomic repetitive sequences. It is thought to emerge from the chromosomes by a mechanism that probably involves homologous recombination. We found that eccDNA level is elevated *in vivo* (in Drosophila) and in mammalian cells in response to DNA damage. We suggest that eccDNA levels can serve as a novel structural DNA indicator for the dynamics of the genome in cancer.

Objectives: In order to determine whether eccDNA levels are related to cancer we first studied the mechanism of its formation, after which we plan to establish experimental tools for translating this information to human cells.

Methods: We used a two-dimensional gel electrophoresis approach to analyze eccDNA. This technique enables the identification of circular molecules within a relatively small sample of total DNA. We tested DNA prepared from Drosophila mutants defective in several recombination and DNA repair genes, as well as in chromatin modifying genes.

Results: The first promising mutants that did affect the level of eccDNA were in the S*pn*A gene. S*pn*A was recently reported as the Drosophila homolog of rad51, which plays an important role in the repair of double-strand breaks. We found that several combinations of *spn*A mutant alleles and a deletion of the gene decreased the levels of eccDNA in adult flies, suggesting its involvement in the formation of eccDNA. We also found that genes known to be important for chromatin structure (e.g., H*istone deacetylase*1, HP1 and S*u*(*var*)3-9) affect the levels of eccDNA *in vivo* in Drosophila. In addition, we detected eccDNA in cultured cells of Drosophila and humans and began to define a new set of specific probes for systematic investigation of human eccDNA.

Conclusions: Both DNA repair machinery and chromatin structure affect the levels of cellular eccDNA. This opens the way for further deciphering the genetic pathway of eccDNA formation in Drosophila, where genetic analysis is simple, and in humans in the context of malignant states.

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