Virus-induced obesity

Frank Greenway
Louisiana State University, Pennington Biomedical Research Center, Baton Rouge, Louisiana

THE HUMAN ADENOVIRUS-36 (Ad-36) was first described in 1980, about the time that the prevalence of obesity began to increase (15). Prevalence of obesity increased by 30% between 1980 and 1990 and by 61% between 1990 and 2000 with no indication that this increase is lessening (12). The reason for this epidemic increase in obesity is not clear, but dietary changes, such as an increase in dietary fructose derived from corn syrup (2), increased food intake (10), and decreased physical activity (11) have all been suggested as potentially playing a role. Infectious agents such as viruses are another possible contributing factor (3).

Support for Ad-36 being a contributor to the obesity epidemic has been accumulating over several years. Ad-36 has been shown to cause obesity in chickens, mice, and nonhuman primates (4, 5, 8). Obese humans have a higher prevalence of serum neutralizing antibodies to Ad-36 (30%) than lean humans (11%), and the antibody-positive obese or nonobese subjects are heavier compared with their antibody-negative counterparts (1). Similarly, when human twins are discordant for antibodies to Ad-36 antibodies, the antibody-positive twin has a higher body mass index (24.5 ± 5.2 vs. 23.1 ± 4.5 kg/m², P < 0.03) (1). Obese humans positive for antibodies to SMAM-1, an adipogenic avian virus (6), are heavier compared with their seronegative obese counterparts (7). However, because avian viruses are not thought to infect humans, this observation has been interpreted as a cross-reaction to a human virus that is antigenically similar (7).

The mechanism by which Ad-36 causes obesity has been explored. Ad-36 accelerates differentiation of preadipocytes to adipocytes in 3T3-L1 cells, and this has been confirmed in human preadipocytes, as well (14). When the open reading frame E4orf1 from the Ad-36 virus was inserted into 3T3-L1 cells, C/EBP-β, PPARγ-2, and glycerol 3-phosphate dehydrogenase were all stimulated compared with the control 3T3-L1 cells, suggesting that the viral gene E4orf1 is responsible for the stimulation of adipocyte differentiation (9).

If Ad-36 is responsible for a significant portion of human obesity, the logical therapeutic intervention would be to develop a vaccine to prevent future infections. If a vaccine were to be developed, one would want to ensure that all the serotypes of human adenoviruses responsible for human obesity were covered in the vaccine. If one could predict the potential of an adenovirus to cause human obesity by using an in vitro assay or even by animal testing, screening of the ~50 human adenoviruses might be accelerated, shortening the time required for vaccine formulation. The article by Atkinson et al. in this issue of the American Journal of Physiology—Regulatory, Integrative and Comparative Physiology (16), suggests that the increased differentiation of 3T3-L1 cells caused by adenovirus type 31 does not necessarily correlate with the development of obesity in chickens. Furthermore, they report the development of obesity in chickens inoculated with Ad-37, a virus that did not show a correlation with human obesity (16). This observation suggests that the development of obesity in chickens is not necessarily predictive of a human adenovirus causing obesity in humans (16).

In addition to Ad-37 causing obesity in chickens, Ad-5 was recently shown to cause obesity in mice (13). Adenovirus Ad-2 does not cause adiposity in animals and does not enhance differentiation of 3T3-L1 or human preadipocytes (14). Ad-37, Ad-31, and Ad-5 have not been tested for increased differentiation in human adipocytes. The experience with Ad-36 suggests that 3T3-L1 cells function as a good model for defining the mechanisms by which human adenoviruses induce obesity in humans, if the virus in question stimulates adipocyte differentiation in human cells. Thus it is possible that human adipocyte differentiation may be a viable in vitro assay to screen for human adenoviruses capable of inducing obesity in humans (Table 1).

Antibody testing in humans suggests that the development of obesity in chickens is not an effective screening tool to identify human adenoviruses capable of causing obesity in humans. The prevalence of antibodies to Ad-2 was not different in 145 obese human subjects compared with 52 lean controls. The prevalence of antibodies to Ad-31 in 152 obese human subjects was not different compared with 49 lean controls. Because there were only 5 of 198 people positive for the Ad-37 virus, its role in the etiology of human obesity seems remote, despite its demonstrated ability to cause obesity in chickens. This may be due to a lower potential for this virus to cause infection. Infectivity of Ad-36 was 100% in studies when chickens were inoculated with this virus, because all animals developed antibodies to Ad-36 (5) but only 71% of the chickens inoculated with Ad-37 developed antibodies (16).

At this point, it appears that Ad-36 is the only human adenovirus associated with human obesity based on human antibody titers. If virus infections are partially responsible for the human obesity epidemic, it will be important to define all the adenovirus serotypes responsible in formulating a vaccine. Screening of large populations for the differential prevalence

Table 1. Adenoviruses effects in human and animal models

<table>
<thead>
<tr>
<th>Virus</th>
<th>Ad-36</th>
<th>Ad-37</th>
<th>Ad-31</th>
<th>Ad-2</th>
<th>Ad-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiation in 3T3-L1 cells</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>Obesity in animal model</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Differentiation in human adipocytes</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>No</td>
<td>?</td>
</tr>
<tr>
<td>Human antibodies higher in obese</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>?</td>
</tr>
</tbody>
</table>

Only adenovirus (Ad)-36 has been shown to accelerate differentiation in 3T3-L1 preadipocytes, cause obesity in animal models, accelerate differentiation in human preadipocytes, and have a higher antibody prevalence in obese humans. Other human adenoviruses have the potential to do some of these things, but only Ad-36 has been shown to stimulate human preadipocyte differentiation and have a higher antibody prevalence in obese humans—?; Unknown.

Address for reprint requests and other correspondence: F. Greenway, Louisiana State Univ., Pennington Biomedical Research Center, Baton Rouge, LA (e-mail: greenwfl@pbrc.edu).
of antibodies to all 50 or more human adenoviruses to define those associated with human obesity is a daunting task. Clearly, an in vitro assay would make the screening process much more efficient.

The article by Atkinson and colleagues (16) suggests that 3T3-L1 cells are not an adequate in vitro model and that chickens are not an adequate in vivo model for screening adipogenic potential of adenoviruses to induce obesity in humans. Human adipocyte differentiation in vitro may hold promise, because to this point only Ad-36 has been shown to be active in that assay (Table 1).

In summary, evidence is accumulating that Ad-36 plays a role in human obesity by stimulation of adipocyte differentiation. Other adenoviruses cause obesity in animals and stimulate 3T3-L1 preadipocyte differentiation, but neither of these findings correlate with the antibody prevalence in obese and lean humans shown with Ad-36. Therefore, human antibody prevalence in obese and lean human populations appears to be the only reliable method to screen adenoviruses for their potential to cause obesity in humans at the present time. An in vitro assay that correlates with human antibody prevalence would accelerate screening of adenovirus serotypes for their potential to induce human obesity. Identifying such an in vitro assay will be important to efficient vaccine development.

REFERENCES