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OBESITY

Ankyrin-B in susceptibility to obesity

Overeating and lack of physical activity are the leading causes of obesity; however, genetics might also be involved. Strong evidence has linked many genetic loci to obesity, but the mechanism remains elusive. A new study has shown that dysfunction of ankyrin-B (a protein expressed by the proposed obesity susceptibility gene *ANK2*) in adipose tissue results in cell-autonomous adiposity by increasing glucose uptake and lipogenesis.

Previous studies by Damaris Lorenzo, Vann Bennett and colleagues found that ankyrin-B mutant mice consumed more glucose and exhibited increased levels of GLUT4 in adipose tissue and striated muscle. Mice deficient in ankyrin-B in only adipocytes showed the same results, suggesting that the observed effects were due to fat cells.

In their new study, Lorenzo and Bennett used *in vitro* binding assays using purified proteins and co-immunoprecipitation to demonstrate that ankyrin-B directly couples GLUT4 to clathrin to promote their association in adipocytes. Dysfunction of ankyrin-B resulted in inefficient GLUT4 return from the cell surface, which was associated with increased glucose uptake and lipogenesis. "Thus, we identified ankyrin-B as a novel clathrin adaptor in adipocytes," says Lorenzo.

Lorenzo and Bennett also identified seven human mutations in ankyrin-B that caused adiposity in an *in vivo* rescue assay in ankyrin-B-deficient adipocytes. These mutations are candidates for susceptibility to obesity in humans. "This work advances our knowledge of the role of the membrane-associated cytoskeleton in cellular and systemic metabolism, and metabolic disease," concludes Lorenzo. "The ankyrin-B variants characterized in this study are cumulatively found in over 6 million Americans of different ethnicities; therefore, dysfunction of ankyrin-B in adipocytes could have broad health effects."

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ORIGINAL ARTICLE Lorenzo, D. N. & Bennett, V. Cell-autonomous adiposity through increased cell surface GLUT4 due to ankyrin-B deficiency. *Proc. Natl Acad. Sci USA* http://dx.doi.org/10.1073/pnas.1708865114 (2017)
FURTHER READING Lorenzo, D. N. *et al.* Ankyrin-B metabolic syndrome combines age-dependent adiposity with pancreatic B cell insufficiency. *J. Clin. Invest.* **125**, 3087–3102 (2015)