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RESEARCH WATCH

Targeting both sides of the GDF15-GFRAL-RET receptor complex: A new approach to achieve body weight homeostasis

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Abstract Obesity is a chronic, complex disease, which is associated with several comorbidities, including diabetes mellitus, hypertension, and cardiovascular diseases. It is estimated that the prevalence of obesity among both adults and children nearly tripled between 1975 and 2016, highlighting a huge unmet treatment need. However, the currently available anti-obesity drugs have serious side effects, which limit their long-term use. The finding that the newly-identified brain GDF15-GFRAL-RET receptor signaling complex is involved in stress/disease-induced anorexia will certainly impact our knowledge of body weight homeostasis under healthy and disease conditions. Based on this breakthrough, a new class of GFRAL/RET-based drugs is highly anticipated for the treatment of obesity, as well as cancer-induced cachexia.

Obesity is a chronic, complex disease, which is associated with several comorbidities, including diabetes mellitus, hypertension, and cardiovascular diseases. According to 2016 WHO data, about one-third of the global population is either overweight or obese. It is estimated that the prevalence of obesity among both adults and children nearly tripled between 1975 and 2016 (http://www.who.int/mediacentre/factsheets/fs311/en/), highlighting a huge unmet treatment need. The present therapies for obese patients include lifestyle modification,

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pharmacotherapy, and surgical intervention. Although lifestyle modification is preferred, its efficacy on weight loss in most of the patients are limited. Surgical interventions such as Roux-en-Y gastric bypass is very effective but it is associated with complications.[1] Most of the available anti-obesity drugs work through CNS neurotransmitter pathways to suppress the patient's appetite so that their food intake can be curtailed. However, weight loss induced by these drugs is modest and some of these drugs have serious side effects, which limit their long-term use. In other cases, there are contradictions due to some obesity-related complications.[2] Therefore, a new class of anti-obesity drugs is strongly desired. In 2007, Johnen et al demonstrated that the anorexia/cachexia that develops in patients with advanced cancer was caused by a member of the TGF-beta superfamily of cytokines, macrophage inhibitory cytokine-1 (MIC-1), also known as growth and differentiation factor-15 (GDF15).[3] The anorectic effect of GDF15 was determined to be mediated through the central nervous system.[3,4] However, the brain receptor that binds and mediates the anorectic signaling by GDF15 remained elusive for the next 10 years. Thanks to a recent breakthrough, the mysterious identity of the brain GDF15 receptor has just been revealed.

Four research groups from different pharmaceutical companies simultaneously published their discoveries in recent issues of *Nature* and *Nature Medicine*.[5–8] Through their independent studies using mice, rats, and non-human primates, these four groups came to the same conclusion that GFRAL (GDNF-family receptor alpha-like) is the high affinity binding receptor for GDF15, which in turn signals through a co-receptor, RET (a receptor tyrosine kinase) to mediate the anorectic effect. This important collective discovery uncovered a previously unknown appetite-control pathway in the brain, which will certainly impact our understanding of body weight homeostasis under normal and stress/disease conditions.

Although multiple studies showed that injecting or overexpressing GDF15 in experimental animals inhibited their food consumption and caused weight loss,[3,6,7,9] using GDF15 ligand as an anti-obesity drug has drawbacks. First, GDF15 has diverse biological roles in gestation, chronic inflammation, and cancer progression, raising the possibility of serious untoward or off-target effects.[10] Second, the cost of GMP production of GDF15 may prove to be financially prohibitive. Third, the need to administer the ligand by injection would be inconvenient for patients. Since GDF15's anorectic effect is mediated through the GFRAL/RET receptor complex, which has an exclusive distribution in the brain, this unique feature can be experimentally exploited to design and screen chemical compounds for agonistic or antagonistic activities specifically targeting the brain GFRAL/RET complex. Hopefully a new class of GFRAL/RET-based drugs will soon emerge for the treatment of obesity. These studies may also yield a treatment for cancer-induced anorexia and cachexia.

Conflict of interest

The authors declare that no conflict of interest exists.

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