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EDITORIAL

HUMAN BODY AS A MULTICRINE GLAND

The present Editorial is a reflection from the article by Stephen Manning (1) and by Sridhar Gumpeny and Lakshmi Gumpeny (2) published in this volume of *Adipobiology*. Focusing to injured *Homo obesus* (1) and glucose and energy homeostasis (2), the authors also discussed adipose- and bone-derived endocrine proteins collectively termed adipokines and osteokines, respectively.

Here, we introduce the term "multicrine" to embodying various secretory phenomena including exo-, endo-, para-, auto-, intra- and juxtacrine, also retrocrine (3,4) and necrocrine (5,6) pathways. Their final products are: enzymes, protein and steroid hormones, cytokines, chemokines, cardiokines, enterokines, adipokines, myokines, and osteokines. For NGF as neurokine, see Rita Levi-Montalcini *et al* in *Trends Neurosci* 1996; 19:514-520; for NGF and BDNF as metabokines, see Chaldakov *et al* in *Riv Psichiatr* 2009; 44:79-87.

Traditionally, the endocrine system consists of glands, each releasing hormones into the bloodstream, whereas the exocrine glands discharging enzymes into the ductstream/lumens. In addition to the "classical" endocrine organs, many other organs that are part of other body systems, such as the heart and kidney, also produce and release endocrine products; for instance, heart secretes natriuretic peptides (see below) and kidney secretes erythropoietin and renin. Certain glands communicate each other in sequence thus creating axis, for example, the hypothalamic-pituitary-adrenal axis. Recently, many other axises have been recognized, e.g. adipose-brain axis, adipose-bone axis, muscle-adipose axis and entero-insular axis (see below).

According to Palade-Blobel's paradigm, the process of protein secretion is mediated by synthesis, post-translational modification and folding, and sorting and targeting to final destinations including plasma membrane, nucleus, intracellular organelles, or exocytosis. Briefly, the three major types of secretory products are plasmalemmal, intracellular (imported) and exported proteins (7,8). Further, non-rough endoplasmic reticulum-Golgi complex pathways using multivesicular endosome-derived exosomes and plasmalemma-shedding microparticles termed ectosomes are also appreciated in the recent studies of cell secretion (Fig. 1).

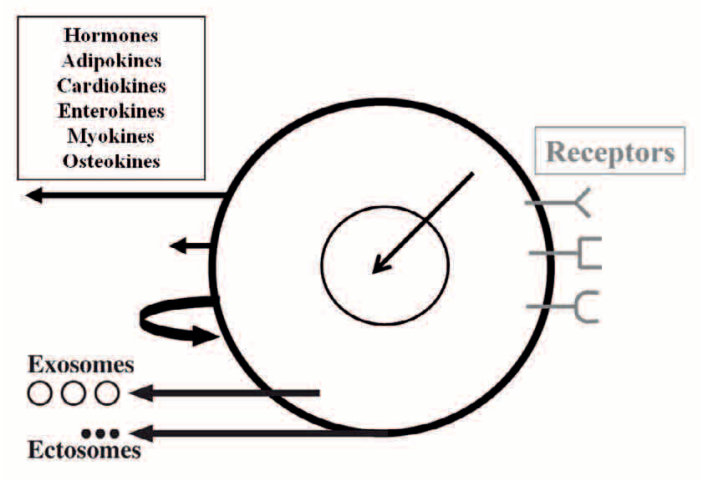

Figure 1. Schematic illustration of a "multicrine cell". The arrows, left from up-to-down, indicate endocrine, paracrine and autocrine pathway; other two arrows show exosomes and ectosomes. The arrow targeted the nucleus indicates an intracrine pathway

Adipose tissue and adipokines

The most momentous challenge that has occurred in the end of 1994 has been the discovery of leptin, an adipocyte-secreted *Ob* gene-encoded protein (9). This became an acute trigger for the current development of adipobiology, particularly the studies on adipose-derived signaling protein designated adipokines (8,10-14).

Diffuse neuroendocrine system and hormones

Historically, Nikolai Konstantinovich Kulchitsky (1856-1925) has identified the enterochromaffin cells found in the crypts of Lieberkuhn of gastrointenstinal mucosa, in 1897. This discovery formed the basis for the subsequent delineation of the diffuse neuroendocrine system (DNES) by Friedrich Feyrter in 1938; examples of DNES include Feyrter's Hellen Zellen (clear cells) in pancreas and gut, hepatic stellate cells (Ito cells), testicular Leydig cells and other cells disseminated throughout the body (15), adipose

tissue (16,17) and circulating immune cells (18,19) being introduced into the DNES. The pro-opiomelanocortin (POMC) gene encodes a family of peptides originally identified in the pituitary gland. An important POMC-derived peptide hormone, corticotropin (ACTH), is also produced by leukocytes (18).

Heart and cardiokines

Knowledge of the cardiac endocrine function was initiated with the discovery of "specific granules" found in the atrial cardiomyocytes of experimental animals examined with transmission electron microscope by Jemieson and Palade (20). Onward, the granules' content was found to consist of two different peptides with similar biological effects: A- and B-type natriuretic peptides (21).

Gut and enterokines

Certain intestinal mucosal cells synthesize and release hormones (enterokines) termed incretins. These include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both of which promote proliferation of pancreatic beta cells and prevent their apoptosis (22). Incretins also contribute to insulin secretion from the beginning of a meal and their effects are progressively amplified as plasma glucose concentrations rise. The current interest in these enterokines is due to the fact that their effects are severely reduced or absent in patients with type 2 diabetes mellitus, thus representing a novel therapeutic target for this disease (23,24).

Skeletal muscles and myokines

Recently, skeletal muscles - in response to contraction - also "became" an endocrine gland. They produce and release interleukin-6 (IL-6), IL-15 and adiponectin (25-30), leukemia inhibitory factor (31, as a paracrine signal), BDNF (32,33) and myostatin, or growth differentiation factor 8 (GDF-8) (34). These molecules are collectively termed myokines. Accumulating findings suggest that myokines may exert specific effects on adipose tissue as well as mediating anti-inflammatory, anti-obesogenic and insulin-sensitizing effects.

Skeleton and osteokines

The skeleton has recently emerged as an endocrine organ with effects on body weight control and glucose homeostasis through the actions of bone-derived signaling protein (osteokines) such as osteocalcin and osteopontin (1,2,35,36). The cross-talk between the adipose tissue and the skeleton constitutes a homeostatic feedback system operating with osteokines and adipokines in a bone-adipose axis (35,36).

Altogether, the human body may be considered a multicrine gland delivering a large number of peptides and proteins (also steroids and other signaling molecules) which control a large scale of biological processes in health and disease.

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