

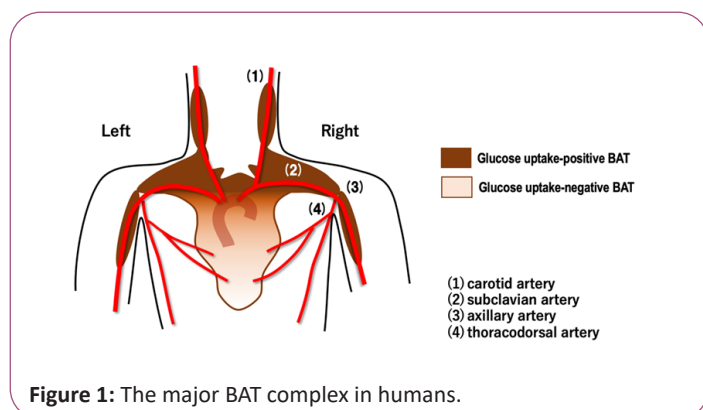
## Evolving Concept of Brown Adipose Tissue in Humans

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### Description

Brown Adipose Tissue (BAT) was first recognized as a heat-producing fat in small hibernating animals. BATs contribute not only to robust thermogenesis after hibernation but also to the maintenance of body temperature under acute cold exposure. They are distributed in specific sites of the body such as cervical, supraclavicular, axillary, paravertebral, periaortic and suprarenal regions. The existence of BAT in humans was described as early as in 1908 in autopsy reports [1], where the interscapular BAT was termed as “interscapular gland” that has cervical, clavicular and scapular processes. Its distribution sites correspond with those of the major arteries in the upper torso (**Figure 1**).



**Figure 1:** The major BAT complex in humans.

After more than one hundred years, human BAT was rediscovered, being driven by the fact that healthy individuals show unexpected radioactive signals in cervical, supraclavicular and axillary regions in <sup>18</sup>F-FDG-PET studies [2-5]. A large volume of evidence has shown that the existence of BATs correlates with healthy metabolic status (example: non-obese, insulin-sensitive). The largest BAT in mice is located in interscapular regions and termed as interscapular BAT (iBAT). Since <sup>18</sup>F-FDG signals in interscapular regions were detected only in infants in humans, the energy source of iBAT may be shifted from glucose to lipid in adult humans. Thermogenic ability of human BATs is activated by beta3-adrenergic stimuli [6] and Atrial Natriuretic Peptide (ANP) signals [7] under physiological conditions. Whether there are still other molecules that activate thermogenesis by BATs remains elusive. Since BATs are hyperactivated under cancer cachexia, certain cancer-related substances may possible serve as BAT activators [8]. Although BATs are distributed separately in the body, they create functional coalition *via* secreting factors [8]. BATs

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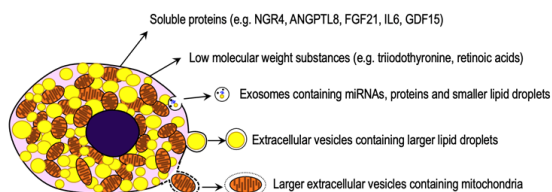
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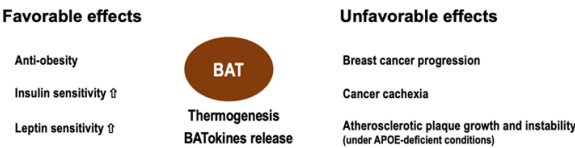
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improve metabolism not only by enhancing energy expenditure *via* heat production but also by producing metabolism-improving secreting factors. BATs produce various bioactive substances, which are collectively called as BATokines. Among the proteins reported to serve as BATokines, only NGR4 and ANGPTL8 shows BAT-specific gene expression profiles [8]. Therefore, there may be still additional BATokines to be discovered. For example, there may be BAT-derived leptin sensitizer(s). It is known that BAT-ablated mice *via* genetic modification showed severe leptin resistance and, as a result, suffered from morbid obesity [9]. By contrast, UCP-1-deficient mice showed only mild leptin resistance without obesity [10]. Therefore, BATs guarantee leptin sensitivity independent of their thermogenic activities and energy expenditure. Besides soluble proteins, BATs produce low molecular weight substances and exosomes, which are shown to contribute to the improvement of metabolism [8]. Furthermore, BATs produce larger sized Extracellular Vesicles (EVs), in which are detected mitochondria [11]. The involvements of those EVs in metabolic improvement in humans are now awaiting to be explored (**Figure 2**).



**Figure 2:** BATs produce various materials.

Although BATs are generally recognized as preferable tissues with anti-obesity and metabolism-improving functions, they may also be involved in promoting unhealthy conditions such as cancer cachexia, breast cancer progression and atherosclerotic plaque growth and instability as shown in APOE-deficient situations [8]. In this sense, BATs may be a double-edged sword (**Figure 3**). In clinically applying BATokines to health promotion, the dose as well as the mode of the usage should be carefully considered.



**Figure 3:** Double-sided aspects of the biological functions of BATs.

BATs are distributed in cervical, supraclavicular and axillary regions, which are adjacent to the main branches of the aortic artery. Not only widely recognized BATokines such as NGR4, ANGPTL8, FGF21, IL6, GDF15, BAT produces various substances including lipids, exosomes and larger extracellular vesicles [11]. BATs exert both favorable and unfavorable effects depending on the situations.