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Letter to the Editor

Is irisin a decisive protein in cancer cachexia and death of cancer cells?

Dear Editor,

Cancer cachexia is a multi-factorial wasting syndrome of the organism where the body loses both fat and skeletal muscle simultaneously. Characterized by weight loss, it can be seen in 50 to 80% of cancer patients depending on the tumor type, and is irreversible[1]. The syndrome involving increased basal energy consumption, anorexia and impaired metabolic condition of the cells, the fundamental units of life, is one which those in the age of omics spare no effort to cure, but to no avail[2]. One cause of cachexia in cancer is the destruction of fatty tissue through lipolysis[3]. In this process, lipid mobilizing factor (LMF) and tumor (and host) factor zinc-alpha-2 glycoprotein directly stimulate the lipolytic effect in adipose tissue, causing cachexia[4]. Due to the changes in the gene expressions of uncoupling proteins in the mitochondrial membrane of their cells, cancer patients consume more energy than healthy individuals during rest[5].

Cancer cachexia may also be associated with irisin. Bostrom et al. have shown that one of the mechanisms of high energy consumption in the organism is increased uncoupling proteins in the brown fatty tissue due to the conversion of white fatty tissue to brown fatty tissue by irisin and the resulting mitochondrial uncouple respiration which leads to heat release without ATP production6. This glycopeptide hormone was first identified in the skeletal muscles (myokine)[6]. Later, it has been also found in almost all tissues (ubiquitously) of eukaryotic organisms[7,8] and released into the blood[9-11], saliva[10,11], milk[12], urine[11] and follicular fluid[13] by cleavage and shedding of the membrane fraction of fibronectin type III domain containing 5 (FNDC5)[14].

Recently, Aydin et al[15] have reported increased irisin expression in the gastrointestinal system (GIS) tissues with cancer, with the exception of liver tissues. Currently, it is not known why irisin does not increase in liver cancers. However, given that irisin inhibits gluconeogenesis[16], liver is the organ where glucose is produced and glucose supplies the energy that cancer cells need (Warburg effect)[15]. If irisin had been elevated in liver cancer, then energy reserves would have been depleted, and this may be the reason why irisin levels do not increase in liver cancer. The incidence of cachexia in upper gastrointestinal cancer is 80%[17]. Therefore, elevated irisin expressions in GIS cancers might have caused cachexia through the mechanism explained above. However, it should be noted that, like a double-edged sword, irisin leads to cachexia on one hand, and prevents the reproduction of cancer cells on the other. It was reported in another study that levels of circulating irisin dropped in breast cancer[18]. Lower irisin levels in the concerned study may be attributed to an effort to control energy consumption, in other words, to save the organism in the cachexia pathway. Various doses of irisin were reported to prevent the reproduction of prostate cancer cells in cell culture experiments[19]. In white fat cell cultures, activating oxygen consumption, irisin causes thermogenesis. It seems that by increasing oxygen consumption, irisin diminishes the oxygen that the tumor cells need and hence contain the division of cancer cells. Lack of oxygen leads to the inhibition of electron transport and oxidative phosphorylation, which in turn reduces ATP production. These data indicate that the organism with cancer has to make a comprehensive evaluation of pros and cons to take a critical decision about the overproduction of irisin or the suppression of its production. In other words, it will either cut back on the production to prevent cachexia or prevent the reproduction of cancer cells by promoting over-secretion of irisin.

Irisin may be preventing the reproduction of cancer cells through the partial heat increase it causes by locally producing heat, as cancer cells are not resistant to heat[15]. It is known that irisin levels are generally elevated after exercise. The incidence of cancer is 30 to 50% lower in individuals who exercise[20]. One possible explanation why cancer is less common in individuals who exercise may be the prevention of the reproduction of cancer cells by elevated irisin after exercise[6,21,22].

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The reduction of the fatty tissue due to lipolysis and muscle wasting observed in the later stages of cancer may be attributed to many tissues' increasing their capacity for irisin synthesis to contain the division of cancer cells. It appears that under such conditions maintenance of energy homeostasis in cancer cells is extremely complex, and hence it is extremely difficult to counteract cachexia. If cachexia is associated with irisin's destruction of fat, this can be prevented by the administration of anti-irisin preparations. However, this will rule out the advantage irisin offers in controlling the division of cancer cells. In this age of omics, the best way to prevent cachexia is to develop multi-faceted therapies aimed at preventing the treatment of cancer.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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