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Perspective

Challenges of Immune Checkpoint Blockade in Cancer T-cell Therapy

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DESCRIPTION

Obesity is now recognized as a devastating medical condition as it increases the risk of various diseases such as heart disease, dyslipidemia, chronic kidney disease, hypertension, Type 2 Diabetes (T2D), stroke and cancer. Progressive exacerbation of Insulin Resistance (IR) and chronic low-grade inflammation. The World Health Organization (WHO) defines overweight and obesity as having a Body Mass Index (BMI) of at least 25 kg/m^2 and at least 30 kg/m^2 respectively, and the prevalence of obesity is significantly increased. It is on the rise and is a major concern around the world. The latest WHO Global Health Report shows that the prevalence of obesity increased by 50% from 2000 to 2016. Specifically, in 2016 he had more than 1.9 billion overweight adults, of which he had 650 million obese adults.

Previously, obesity was described only as an energy imbalance over time. This is due to excess energy storage and accumulation of Adipose Tissue (AT) compared to energy expenditure. Nevertheless, since AT is a highly active endocrine organ that plays a central role in regulating metabolic and immunological homeostasis, obesity is now attributed to widespread dysfunction of AT and is a multifactorial disease. Is considered as increased obesity is associated with changes in the tissue's physiological profile. Obesity-associated spread of fat depot dysfunction is associated with hyperinsulinemia, dyslipidemia with excessive release of Free Fatty Acids (FFA), adipocyte hypoxia, and accelerated cell death due to insufficient oxygen supply, and lead to the accumulation of inflammatory mediators.

Preadipocytes, fibroblasts, endothelial cells, immune cells, and mature adipocytes are the major cell types that make up the AT. Four different types of adipocytes have already been described.

White, beige, brown, pink. These cells differ in morphological and physiological properties. Brown Adipose Tissue (BAT) and White Adipose Tissue (WAT) are the best described types of AT in the literature because they are constitutively present in organisms. White adipocytes, which are predominant in WAT, are characterized by unilocular lipid droplets, small and sparse mitochondria, and are classically involved in energy uptake signaling and storage. In contrast, BAT is composed primarily of brown adipocytes, characterized by multilocular lipid droplets and abundant mitochondria expressing high levels of Un Coupling Protein 1 (UCP1). As such, BAT is involved in thermogenesis (non-shivering thermogenesis) and weight loss, and exhibits changes throughout an individual's lifetime. BAT is maximally recruited at birth, switching dramatically from a quiescent to a most activated state with respect to heat production to provide thermoregulation, and is located in the interscapular region of neonates and small mammals. During infancy, BAT decreases as individuals are already exposed to cold and thermogenesis from skeletal muscle shivering begins. There is evidence that the amount of BAT may temporarily increase near puberty, suggesting that BAT is involved in other functions than replacing the missing shivering thermogenic process. In adulthood, less basal activity of BAT is detected, and cold stimulation of this tissue may be significantly reduced after middle age with decreased expression of UCP1. In particular, BAT tends to change morphologically over time towards a more distinct lipid storage profile, highlighting changes in BAT composition and function over the mammalian lifetime.

The AT is so plastic that it can be expanded and rebuilt. AT expansion may be the result of hypertrophy, hyperplasia, and adipocyte differentiation, and is sensitive to external factors such as diet and exercise routines. AT type can undergo Tran's differentiation. BAT can convert to an intermediate beige phenotype through a process called lightening. The reverse process also occurs. The conversion of WAT to brown-like AT is the result of a process called tanning. Sunburn occurs in response to cold exposure, increased exercise, the action of pharmacological molecules, and changes in the diet itself. Triggers an intra-signaling cascade. Changes in cAMP levels are detected by protein kinase A (PKA), leading to activation of mitogen-activated protein kinases, catabolic reactions that convert triglycerides to Fatty Acids (FA), and activation and upregulation of UCP1. Brings, allowing the decoupled production of ATP and heat dissipation. Sunburn and BAT activation are currently being investigated as promising therapeutic strategies for obesity.

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