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A Review on differential effects & dichotomy of adipose tissue macrophages(ATMs) on obesity induced cancers

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Abstract

Overweight and Obesity are terms frequently used as synonyms. According to the World Health Organization (2017), obesity prevails aggressively worldwide. According to National Cancer Institute, endometrial cancer (two to four times), esophageal adenocarcinoma (twice), gastric cardia cancer (twice), liver cancer (twice), kidney cancer (twice), multiple myeloma (10-20%), meningioma (twice), pancreatic cancer (1.5 times), colorectal cancer (30%), gall bladder cancer (60%), breast cancer(maximum 40%), ovarian cancer (10%) and thyroid cancer (10%) are some of the types which mostly came across in lives of obese people as compared to people with healthy BMIs. Macrophages are plentiful in the tumor micro milieusand more than other types, TAMs are associated with malignancies. This review aims to recapitulate the different types and functions of ATMs and their role in associated cancer pathogenesis.

Keywords: TAM, ATM, Cancer, Cardia.

Introduction

A body mass index (BMI) of 25 accounts for being overweight and 30 defines obesity. BMI (body mass index) is the mass per height ratio in kg per meter square. For children under the age of five, the WHO child growth standards median is a tool for the measurement of BMI. According to the world health organization fact sheet updated at end of 2017, the obesity ratio almost tripled from 1975 to 2016. In 2016, up to 1.9 billion adults were overweight, and out of these, more than 650 million fell in the range of obesity. Almost 39% and 13% of adults were overweight and obese, respectively, in 2016. High energy-dense meals, urbanization, sedentary transportation modes, and deskbound jobs, all lead to these high percentages of obesity. Raised BMIs in turn leads to high percentages of CVS and musculoskeletal problems as well as cancers. In 1892, the term macrophage was used by Metchnikoff for large cells engulfing unwanted and unnecessary particles and old worn-out cells. Macrophages are indifferently present in all vertebrate and invertebrate organisms. These assorted cells are disseminated in many different tissues in humans and animals. They usually exhibit heterogeneous cellular morphological properties and have variable duties according to the need of their home environments. They

exhibit diversified evolutionary maturity patterns (Metchnikoff, 1892).

Literature Review

The mononuclear system of phagocytes is mainly dependent on monocytes, phagocytic macrophages, and dendritic cells. All of these present inconsistent morphological characters. These are developed from hematopoietic stem cells. These stem cells are commonly found in bone marrow excessively and are later termed as monocytes. Monocytes once produced, are released into circulatory system, from where these cells are taken up as required by neighboring tissues. These cells are then differentiated into adult macrophages and bear accountability of immunity surveillance phagocytosis, antigens presentation, and cytokines secretion (Murray & Wynn, 2011). Macrophages are conservatively divided into two subtypes: M1 and M2. Lipopolysaccharides and gamma interferons are the two receptor ligands that are responsible for M1 macrophages activation while M2 is the macrophages that are activated by the 4th and 13th interleukins (IL-4 and IL-13). These two can also be differentiated in the sense of expressions they produce (Murray & Wynn, 2011). Activated macrophages are better described by three populations i.e., classically activated macrophages (up-regulated by IFNγ), wound healing macrophages (up-regulated by IL-4 and some of its markers are suppressed by IFNγ), and regulatory macrophages (initiated by TLRs and other stimuli) (Mosser & Edwards, 2008). Classically activated macrophages are produced by cell-mediated immunity and are also produced transiently in stress or viral attacks (Dale, Boxer, & Liles, 2008). However, pathogens have developed resistance and they disturb the gamma interferon signals to activate macrophages. These cells are vital in immune responses, but if remained uncontrolled, these may lead to auto-immune reactions. Classically activated macrophages are the key factors in rheumatoid arthritis (Szekanecz & Koch, 2007), ulcerative colitis, and Crohn's disease (Zhang & Mosser, 2008). The first adaptive immune signal in case of wound or injury is Interleukin-4, primarily produced by basophils, other granulocytes, and mast cells. Interleukin-4 is also produced by some parasitic and fungal biopolymeric components like chitin. This signal promotes the conversion of resident macrophages to wound healing macrophages. In wound healing macrophages, arginine is converted to ornithine which is the predecessor molecule for polyamines and extracellular matrix collagen, hence contributes to wound healing (Gallagher et al., 2007). Regulatory macrophages are up-regulated by two signals; the first signal (toll-like receptors TLRs) has a very minute role in activation but is necessary for combination with second stimuli or immune complexes. Regulatory macrophages usually proceed with wound healing macrophages. Next to these three populations are tumor-associated macrophages (TAMs) which share characteristics of regulatory macrophages and wound-healing macrophages. In obese individuals, macrophages share characteristics of wound-healing macrophages and also have a transit of classically activated macrophage-like activities (Mosser & Edwards, 2008). A newly proposed classification describes M1 as type-1aATMs and M2 as type-2ATM. Type-1b ATMs and type 3 ATMs are newly added classes to ATMs of animals, while humans lack type-3ATM phenotypes. Shaul et al (2010), isolated type-1a and type-1b of ATMs from obese mice which presented the mixed M1 and M2 traits. All of these ATMs subtypes have tendencies of anti-inflammatory and homeostatic profiling like the M2 subtype (Shaul, Bennett, Strissel, Greenberg, & Obin, 2010). Zeyda and coworkers

worked on mice, grew on high-calorie food which made them obese, and then they isolated type-1a, type-2, and type- 3 ATMs from those mice. The type-2 ATMs did not show activities resembling the M2 subtype at all. Additionally, these type-2 ATMs were presenting positive inflammatory responses by the production of chemokines to counteract obesity and related inflammations. This led to the need for further investigation of ATMs phenotypes and characterization (Zeyda et al., 2010). ATMs in obese individuals exist in form of crown-like structures (CLSs), that are accumulations of ATMs around dead adipocytes (Cancello et al., 2005; Kamei et al., 2006; Lumeng, Bodzin, & Saltiel, 2007). CLSs are not found in lean models. These CLSs secrete TNF- α which is responsible for inflammation in obese bodies. CLS also contains lipid particles which give them a resemblance to foam cells of atheromatous plaques (Kosteli et al., 2010; Lumeng, Deyoung, Bodzin, & Saltiel, 2007; Prieur et al., 2011). Lumeng et al. presented an in vivo study and labeled two kinds of ATMs, one as outsider macrophages which were migrated as well as recruited newly and another local old inhabitant macrophages. The earlier type ATMs show CD11c surface marker but later do not. The earlier are also differentiated from later in expression as they show high levels of IL-6 and TNF- α whereas residential ATMs have high levels of MGL-1 only. TAMs have a crucial role in the induction of malignancies. Vascularization of tumor entities is necessary if tumors are to grow more than 2-3 cubic mm and to spread to other organs. An increase in tumor cell mass leads to hypoxic conditions which in turn produces inflammatory mediators, that ultimately cause recruitment of macrophages and more M2 macrophages than M1(Siveen & Kuttan, 2009). From tumors to metastatic conversion, monocytes continuously gain access to tumor masses via blood circulation. This recruitment and infiltration are activated by many chemoattractants (like CSF-1, CC chemokines, CCL2-CCL, and VEGF) produced by tumor cells (CSF-1 is colony-stimulating factor-1 and VEGF is vascular endothelial growth factor), and the level of these chemicals is proportional to TAMs in tumors (Murdoch, Giannoudis, & Lewis, 2004).

Association of obesity with different types of cancers

- Endometrial cancer is the most widespread cancer in the US, its incidence and succession both are linked to ATMs. Privileged allocation of adipose tissue in the belly favors risk of endometrial cancer, and other intra-abdominal tumors (Klopp et al., 2012). Other than Quetelet's index(kg/m2), age at menarche, diabetes, HTN, and some other related medical conditions are some of the factors governing endometrial cancers(La Vecchia, Decarli, Fasoli, & Gentile, 1986). The risk of endometrial cancer in obese women is much more than in cohort lean women. The continuous high-level mutagenic stimulation of endometrium by chronic estrogen is the major factor while endometrium cells differentiation is not well mediated by progesterone(Lacey Jr et al., 2008). Prolactin and TSH also play role in it (Fader, Arriba, Frasure, & von Gruenigen, 2009). In a study, Omentum adipose stromal cells (O-ASC) and subcutaneous adipose cells (SC-ASC) were isolated and characterized for facilitation in endometrial cancer. The study revealed that O-ASC favored the growth and vascularization of endometrial cancer more than SC-ASC even though bothof these reside in tumor cells equally well (Klopp et al., 2012).
- Esophageal cancer is 8th in spread according to global cancer statistics and 6th source of morbidities worldwide (Parkin, Bray, Ferlay, & Pisani, 2005). The

insulin-like growth factor -1 axis(IGF-1 axis) is secreted in high quantities by adipocytes and their precursors and are required for the maturation of preadipocytes (Blüher, Kratzsch, & Kiess, 2005). It has documented effects on malignant cell proliferation and maturation and also on insulin-associated obesity dysregulations (Samani, Yakar, LeRoith, & Brodt, 2007). IGF-1 axis is the key link between obesity, esophageal, and other gastrointestinal cancers (Doyle et al., 2012).

- Breast cancer is the second most common type in women and the first most common around the world (Trentham-Dietz et al., 2000). In obese postmenopausal women, the risk of breast cancer incidence is 50% increased due to raised estradiol (Trentham-Dietz, Newcomb, Nichols, & Hampton, 2007). This positive association is also contradicted by some studies which hypothesized the mechanisms of altered sex hormones, distorted growth factors, and the role of cytokines in developing this link (Pischon, Nöthlings, & Boeing, 2008). Some studies had also given the perspective that circulating estrogens are protective agents against breast cancers (Suba, 2013). Obesity may also induce breast cancers by IGFs related pathways (Frasca et al., 2008).
- The occurrence rate of Colorectal cancer is ten times more in developed countries and the third most common cancer globally (Key et al., 2004). Colorectal cancers and obesity are positively related (Bergström, Pisani, Tenet, Wolk, & Adami, 2001).
- Obesity and prostate cancer have shown a slight correlation only (MacInnis & English, 2006).
- Primary liver cancer is the third most common cause of death. Its prevalence is rising day by day and hepatocellular cancer is now at the fifth number in the global cancer statistical approach (El–Serag & Rudolph, 2007). In the two most evident liver mortalities i.e., alcoholic cirrhosis and cryptogenic cirrhosis, obesity is a definite factor for hepatocellular carcinoma (Nair, Mason, Eason, Loss, & Perrillo, 2002).

Conclusion

Adipose tissues occur throughout the body as brown fat (in paraspinal and supraclavicular areas), ectopic hepatic fat, pericardial, perivascular, visceral, subcutaneous, and bone marrow fat tissues (Fuster, Ouchi, Gokce, & Walsh, 2016). All Macrophages represent differences in anatomy and functionality and the same is the case with ATMs (Gordon & Taylor, 2005). ATMs are most frequently inhabitant leukocytes of adipose tissues (Garg, Delaney, Shi, & Yung, 2014). High BMIs are linked with high chances of ordinarily spread and widespread malignancies in sex-dependent and site-dependent manners. Insulin and Insulin-like growth factor-I axis, sex steroids, adipokines, obesity generated hypoxia, shared genetic vulnerability, and wander adipose stromal entities represent some hypotheses trying to explain this linkage. However, no single mechanism can be proposed (Roberts, Dive, & Renehan, 2010). In the same manner, losing weight is associated with a low cancer incidence rate (Basen-Engquist & Chang, 2011). TAMs play vital roles in malignancies i.e., tumor invasion, growth, angiogenesis, metastasis, and immunosuppression (Lewis & Pollard, 2006). Tumor-associated macrophages contribute towards metastasis by induction of tumor milieu and new blood vessels growth. Macrophages had proved themselves as therapeutic targets clinically because they have more stabilized genetic makeups than carcinogenic cells (Cook & Hagemann, 2013). A lot more work is still required to

understand the classes and physiology of ATMs, to control and prevent adiposity-induced cancers effectively.

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