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ORIGINAL ARTICLE

Diminished immune response to vaccinations in obesity: Role of myeloid-derived suppressor and other myeloid cells

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Summary Obesity is a chronic inflammatory condition associated with an increased production of cytokines and exacerbated immune response. However, obese subjects are susceptible to infections and respond poorly to vaccines. This study evaluated the immune responses of obese mice and the underlying mechanisms by exploring the roles of myeloid cells. Diet-induced obese (DIO) mice were prepared from C57BL/6J mice fed a high-calorie and high-fat diet for 12 weeks. Humoral and cellular immune responses of DIO mice to a hepatitis B vaccine containing the hepatitis B surface antigen (HBsAg) were assessed in sera and via a lymphoproliferative assay, respectively. The effects of $CD11b^{+}GR1^{+}$ myeloid-derived suppressor cells (MDSC) and $CD11b^{+}GR1^{-}$ non-MDSC on T cell proliferation and cytokine production were compared via a cell culture system. The production of cytokines, expression of activation and exhaustion markers, and proportions of apoptotic T cells were estimated with flow cytometry. Increased T and B lymphocyte proliferation and higher interferon-γ and tumor necrosis factor-α levels were detected in spleen cells and liver

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non-parenchymal cell cultures of DIO mice compared to controls ($p < 0.05$). However, antibody to HBsAg (anti-HBs) levels and HBsAg-specific T cell proliferation were significantly lower in DIO mice compared to controls ($p < 0.05$). The addition of MDSC, but not non-MDSC, induced a decrease in HBsAg-specific T cell proliferation, lower cytokine production, decrease in T cell activation, and increase in T cell exhaustion and apoptosis ($p < 0.05$). MDSC play an important role in mediating impaired antigen-specific immunity.

Introduction

The World Health Organization has reported that that in 2008, 1.5 billion adults, 20 and older, were overweight. Of these over 200 million men were obese. Overweight and obesity are the fifth leading risk for global deaths [1]. At least 2.8 million adults die each year as a result of being overweight or obese. In addition, 44% of the diabetes burden, 23% of ischemic heart disease burden, and between 7% and 41% of certain cancer burden are attributable to overweight [1]. Obesity and its comorbidities, including insulin resistance, type 2 diabetes mellitus, atherosclerosis, coronary heart disease, and non-alcoholic fatty liver diseases (NAFLD), have already reached worldwide epidemic proportions [2,3]. Obesity is also associated with an increased risk of numerous types of cancer, as described by a meta-analysis conducted on a total of 282,000 patients with over 133 million person-years of follow-up [4].

The pathological processes involved in obesity are associated with chronic inflammation that is systemic in nature. Obesity-induced inflammation appears to be initiated within adipose tissue, as it expands due to excess fat and caloric intake, and involves the activation of inflammatory pathways in cells that sense fatty acids and cytokine signaling [5,6]. These receptors were originally thought to be involved in only sensing pathogens, but recently were found to also sense fatty acids [7—9].

Despite harboring an inflammatory mucosal milieu, obese subjects exhibit impaired immune responses to specific antigens, such as vaccines. Reduced tetanus antibody titers have been documented in overweight children [10], and impaired immunogenicity of hepatitis B vaccine has been reported in obese persons [11]. Moreover, lower magnitudes of vaccine-induced immunity have been also documented in murine models of obesity [12—15].

However, there is a lack of information regarding the mechanisms underlying the upregulation of certain inflammatory immune responses and down-regulation of antigen-specific immune responses in obesity. A series of studies have suggested that altered functional capacities of lymphocytes, natural killer cells, natural killer T cells, and dendritic cells (DC) may account for the differences in immune function in obesity [13—18]. However, little is known about the role of macrophages and myeloid cells in obesity, which constitutes an evolutionarily conserved defense system that is located at the ports of entry for pathogens and form the first line of defense against environmental threats to the body. In order to dissect the mechanisms responsible for the impaired responses of obese subjects to vaccines, attention needs to be focused on macrophages and myeloid cells, as they traditionally produce abundant amounts of inflammatory mediators, such as tumor necrosis factor (TNF)-α and interferon (IFN)-γ, and are well known for maintaining the inflammatory mucosal milieu [19—21]. Recent studies in cancer patients and animal models of cancer and chronic infections have identified a heterogeneous immature myeloid cell population that is induced by inflammation, and causes immunosuppression [22—24]. These immature myeloid cells are regarded to as myeloid-derived suppressor cells (MDSC). MDSC co-express Gr-1 and CD11b in rodents, whereas traditional macrophages or typical myeloid cells that produce inflammatory cytokines express CD11b, but not Gr-1 ($CD11b^{+}Gr1^{-}$ myeloid cells) [19—24].

We postulated that MDSC may have a role in the diminished antigen-specific adaptive immune response in obesity. To address this issue, we prepared an animal model of obesity by providing high-fat and high-calorie diet to C57BL/6J mice. Antigen-specific humoral and cellular immune responses to the hepatitis B (HB) vaccine were evaluated and compared between obese mice and control mice, which received normal laboratory chow. Since the antigen-specific humoral antibody and cellular immune responses levels were significantly lower in obese mice compared to control