High-fat diet consumption is one of the most important environmental factors leading to obesity, a global health problem that affects more than 300 million individuals worldwide. Saturated fatty acids induce the activation of TLR4-dependent innate immune response, which induces an inflammatory response releasing proinflammatory cytokines and contributing to insulin resistance. A recent study showed that the absence of a functional TLR4 only in bone marrow-derived cells is sufficient to protect mice from diet-induced insulin resistance and defective regulation of whole body energy homeostasis. Using a bone marrow transplant approach, TLR4 loss-of-function mutant and wild-type mice were applied producing chimeras carrying TLR4 either in bone marrow-derived cells or except in bone marrow-derived cells. Mice were fed on high-fat diet or standard rodent chow for eight weeks. Only TLR4 in bone marrow-derived cells induced insulin resistance and increased expression of inflammatory markers in peripherals tissues after high-fat feeding, suggesting that TLR4 expression in bone marrow-derived cells plays an important role in obesity-induced insulin resistance.

**Keywords:** Obesity; insulin resistance; Toll-like receptor 4

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**Introduction**

Obesity epidemic and overweight increases the chance of mortality from diabetes mellitus type 2 complications, cardiovascular events, hypertension, respiratory failure and some types of cancers [1,2]. It is already known that immune cells mediate tissue inflammation during obesity by activating proinflammatory pathways in insulin responsive organs such as liver, white adipose tissue, and skeletal muscle contributing to insulin resistance and type 2 diabetes development [3, 4, 5, 6]. Saturated fatty acids and lipopolysaccharide (LPS) induce TLR4-dependent innate immune signaling transduction, which can trigger two different events: 1) Nuclear factor-κB (NfkB) signaling activation and increased release of proinflammatory cytokines and chemokines such as TNFα, IL1β, IL6 and MCP-1 [7, 8, 9, 10] and 2) IRS1 and IRS2 phosphorylation in serine residues impairing insulin signal transduction [11]. It raises a question if the TLR4-dependent injury in insulin pathway is mediated by TLR4 activation in immune-derived cells and/or in insulin responsive tissues. This question was partially explored in studies that performed bone marrow transplantation (BMT) using TLR4 knockout (TLR4 KO) mice to produce chimeras carrying or no TLR4 in entire body or in cells originating from bone marrow, however the results were conflicting [12, 13, 14]. Recently, Razolli et al. [15] expanded these studies by employing BMT between TLR4 loss-of-function (C3H/HeJ) and wild-type (C3H/HePas) mice confirming that the presence or absence of TLR4 in bone-marrow derived immune cells is able to induces or protect animals from diet-induced insulin resistance, respectively.
TLR4 in cells derived from bone marrow is able to determine weight gain and impairment of whole body insulin responsiveness.

Saturated fats-mediated insulin resistance occurs through toll-like receptor 4 activation. In Razolli et al. study, wild-type (C3H/HePas) and TLR4-loss of function mutant (C3H/HeJ) mice were submitted to irradiation using 8 Gy dose in cobalt 60 source followed by bone marrow transplantation. TLR4-mice carrying a loss of function mutation received bone marrow from Wild-type (WT) mice carrying a functional TLR4 and vice-versa, producing chimeras harboring TLR4 in bone marrow-derived cells only or in whole body except cells originating from bone marrow. After recovery, mice received rodents chow or high fat diet (HFD) containing 60% of calories from fat for eight weeks. Upon HFD, chimeras carrying a TLR4-loss of function in bone marrow-derived cells were protected from increased weight gain by a mechanism dependent on energy expenditure, showed by increased energy efficiency and increased relative expression of uncouplin protein 1 in BAT. The absence of Toll-like receptor 4 in chimeras improved glucose tolerance, insulin sensitivity and restore AKT phosphorylation in liver and white adipose tissue. On the other hand, WT chimeras fed on HFD increased body mass and became obese, followed by glucose intolerance and impairment of AKT signal transduction after insulin stimulus in liver and adipose tissue.

TLR4 in bone marrow-derived cells promote hepatic steatosis and increased cytokines and chemokines expression in peripherals tissues.

Diet-induced low-grade inflammation and ectopic lipid metabolites installation are involved in insulin resistance development. Liver ectopic lipid accumulation is the mainly cause of Nonalcoholic fatty liver disease (NAFLD), an obesity-associated disease [16]. Razolli et al. showed that TLR4 absence in bone marrow-derived cells protected mice from increased triglycerides content and fat liver accumulation as well protected mice from gluconeogenic enzymes PEPCK and G6Pase increased expression in liver after being fed on saturated fat-diet. Also, the absence of toll-like receptor 4 in bone marrow-derived cells was able to prevent mice from increased releasing of inflammatory cytokines TNFα, IL1β, IL6 and MCP-1 chemokine in liver and white adipose tissue. In an opposite way, IL10 anti-inflammatory cytokine expression was increased in mice lacking TLR4 in cells originating from bone marrow in peripherals tissues after HFD. The association between an increased anti-inflammatory signaling and reduced recruitment of pro-inflammatory cells in peripherals tissues of mice carrying a TLR4-loss of function in immune cells originating from bone marrow suggests that toll-like receptor 4 expression in bone marrow-derived cells is sufficient to induce inflammation and fat liver accumulation contributing to insulin resistance during obesity.

Conclusion

In summary, the study of Razolli et al. used a different and expanded approach to show that most of the effect of TLR4 activation in diet-induced insulin resistance depends on the receptor expressed in cells originating from the bone marrow. As TLR4 plays an important role in the activation of an innate immune response against Gram-negative bacteria, long-term targeting of TLR4 in bone marrow-derived cells as an approach to treat type 2 diabetes must be considered with caution.

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Conflict of Interest

The author declares that there is no conflict of interest.

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