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Genome-wide analysis reveals TNFAIP8L2 as an immune checkpoint regulator of inflammation and metabolism

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ABSTRACT

The interplay between inflammation and metabolism is widely recognized, yet the underlying molecular mechanisms remain poorly characterized. Using experimental database mining and genome-wide gene expression profiling methods, we found that in contrast to other TNFAIP8 family members, TNFAIP8L2 (TIPE2) was preferentially expressed in human myeloid cell types. In addition, Tnfaip8l2 expression drastically decreased in lipopolysaccharide (LPS)-stimulated macrophages. Consequently, Tnfaip8l2 deficiency led to heightened expression of genes that were enriched for leukocyte activation and lipid biosynthesis pathways. Furthermore, mitochondrial respiration rate was increased in Tnfaip8l2-deficient macrophages, as measured by Seahorse metabolic analyzer. Taken together, these results indicate that Tnfaip8l2 serves as a "brake" for immunometabolism, which needs to be released for optimized metabolic reprogramming as well as mounting effective inflammatory responses. The unique anti-inflammatory and metabolic-modulatory function of TNFAIP8L2 renders it a novel therapeutic target for cardiovascular diseases and cancer.

1. Introduction

There are four members in the TNFAIP8 (TNF alpha induced protein 8) family, which includes TNFAIP8, TNFAIP8L1 (TIPE1), TNFAIP8L2 (TIPE2), and TNFAIP8L3 (TIPE3). We found recently that germline deletion of TNFAIP8L2 causes fatal inflammation and hypersensitivity to Toll-like receptor stimulation (Sun et al., 2008). Crystal structure of TNFAIP8L2 reveals a unique structural fold, which is shared by all members of the TNFAIP8 family, with no significant homology to other known proteins (Zhang et al., 2009). Although TNFAIP8L2 has emerged as a critical regulator of immunity that maintains immune homeostasis, its additional cellular function and the mechanisms of its action are poorly understood.

Recently, there has been considerable interest in the role of cellular metabolism as a central regulator of immunity. In adaptive immune cells, induction of *de novo* fatty acid synthesis is essential for activation-induced proliferation and differentiation of effector T cells (Kidani et al., 2013; Berod et al., 2014), while fatty acid catabolism via β-oxidation is important for the differentiation of regulatory T cells (Michalek et al., 2011). The role of fatty acid metabolism in innate immune cells, however, is controversial (Huang et al., 2014; Nomura et al., 2016). *De novo* fatty acid synthesis was proposed to support fatty acid oxidation that is required during M2 macrophage differentiation. However, it was recently demonstrated that fatty acid oxidation is dispensable in early activation of M2 macrophages. Thus, the role of fatty acid metabolism in immune cells, especially in the innate immune cells such as macrophages, remains to be elucidated.

In this study, we tested a novel hypothesis that TNFAIP8L2 is involved in metabolic regulation in the immune cells. Using microarray analysis and experimental database mining method, we found that TNFAIP8L2 is exclusively expressed in myeloid cells. TNFAIP8L2 gene expression is reduced in response to proinflammatory stimuli in macrophages, which serves as an immune "brake" molecule that inhibit inflammation, lipid biosynthesis genes, and mitochondrial respiration. Thus, TNFAIP8L2 is an immune checkpoint molecule in myeloid cells and targeting TNFAIP8L2 may serve as a novel therapeutic target for inflammatory and metabolic diseases.

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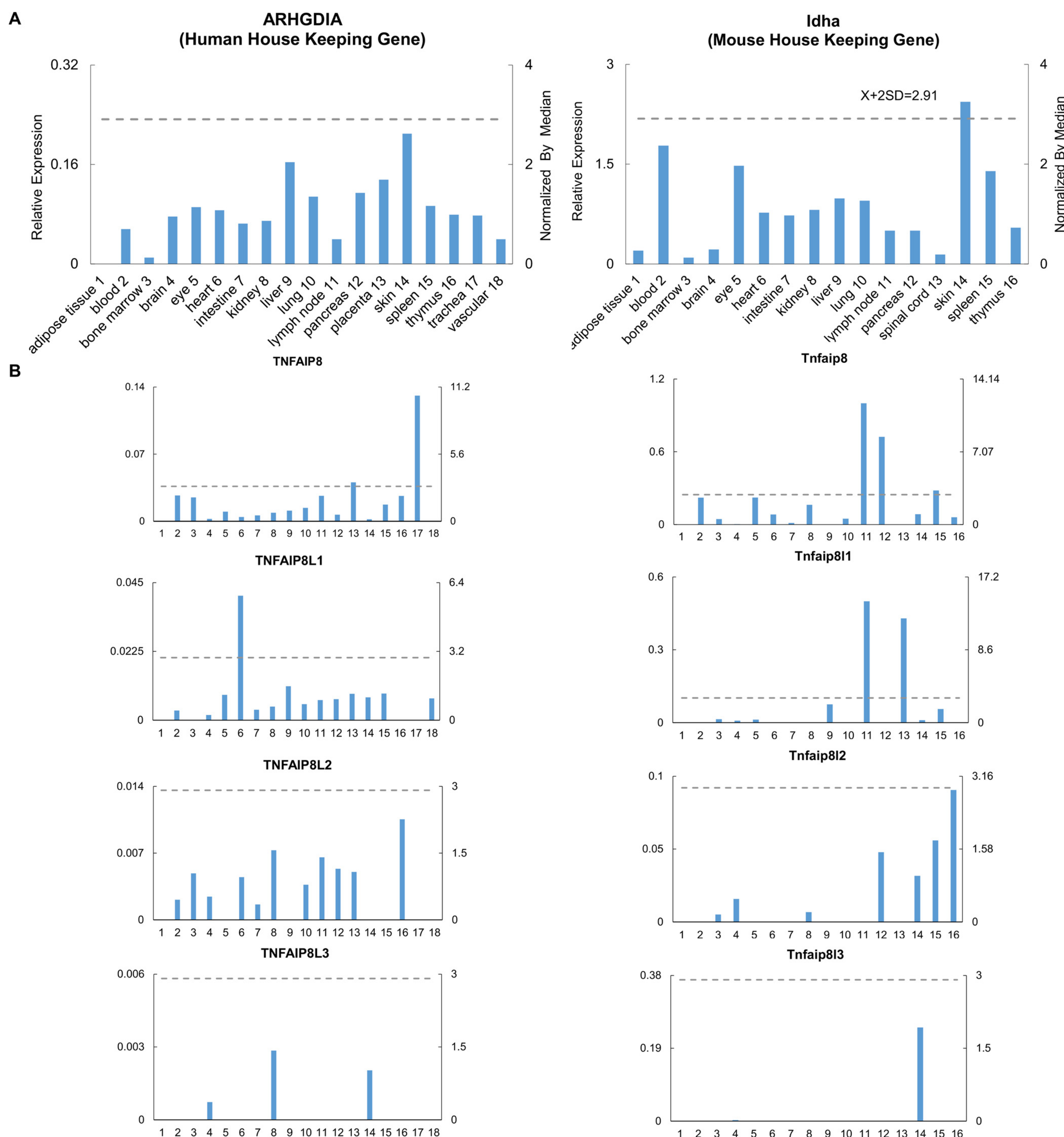

Fig. 1. The gene expression profiles of TNFAIP8 family members in human and murine tissues. A. Data presentation format (The data presented in X-, Y-axis, and tissue order of ARHGDIA and Idha are applied to all the human and mouse genes examined respectively). As an example, the gene expression profiles of human housekeeping gene Rho GDP dissociation inhibitor (GDI) alpha (ARHGDIA) in the eighteen tissues are presented, with the tissue names and position numbers shown on the X-axis. The gene expression data were normalized by the β-actin (Hs. 520640) expression data from the same tissue, which are presented on the left Y-axis. The expression ratios among tissues were generated by normalizing the arbitrary units of the gene in the tissues with the median level of the arbitrary units of the gene in all the tissues which are presented on the right Y-axis. In order to define confidence intervals for statistically higher expression levels of given genes, we calculated the confidence intervals of tissue expression for three housekeeping genes [the mean X + 2 x standard deviations (SD) = 2.83] including ARHGDIA (Hs. 159161), glyceraldehyde-3-phosphate dehydrogenase (GAPDH, Hs. 544577), and ribosomal protein S27a (RPS27 A, Hs. 311640). The expression variations of given genes in tissues, when they were larger than 2.83-fold, were defined as the high expression levels with statistical significance (the right Y-axis). To define confidence intervals for statistically higher expression levels of given genes in 14 mouse tissues, we calculated the confidence intervals of tissue expression [the mean X + 2 x standard deviations (SD) = 3.0] for three mouse house keeping genes including Lactate dehydrogenase A (Ldha, Mm. 29324), non-POU-domain-containing octamer binding protein (Nono, Mm. 280069), and ribosomal protein L32 (Rpl32, Mm. 104368). The expression variations of given genes in tissues, when they were larger than 3.0-fold, were defined as the high expression levels with statistical significance (the right Y-axis). B. The expression profiles of TNFAIP8 family in human (Left column, with TNFAIP8 protein with capital letters) and mouse (right column, with Tnfaip8 protein designated with lowercase letters) tissues.

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