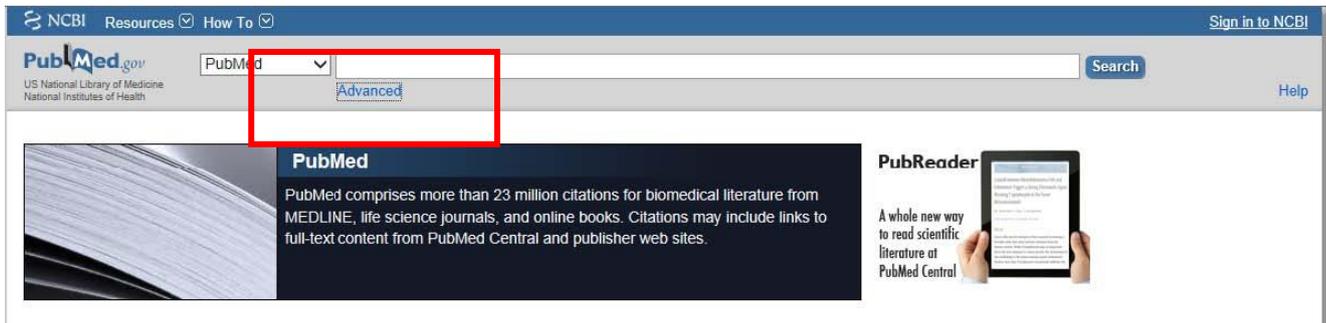


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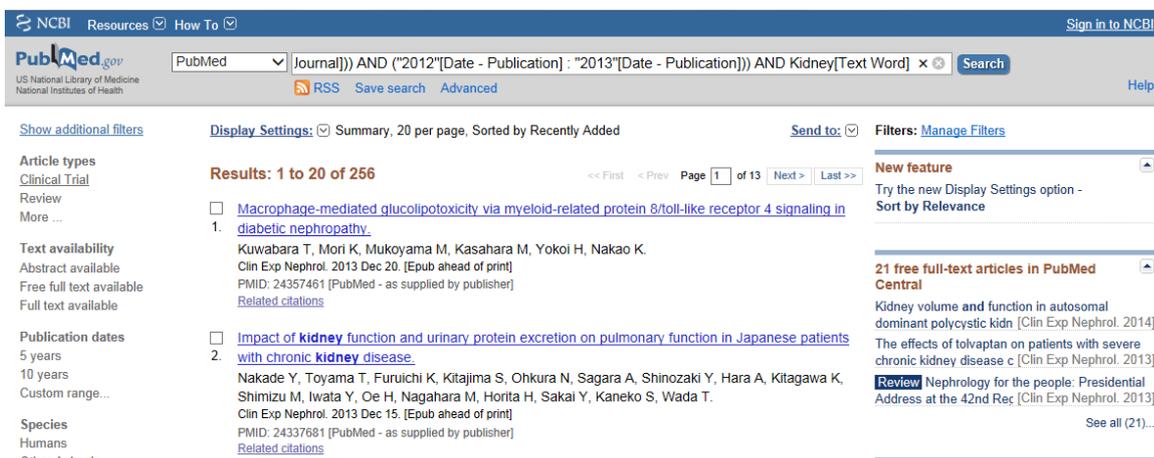
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Clinical and Experimental Nephrology December 2013 Open Access

Macrophage-mediated glucolipototoxicity via myeloid-related protein 8/toll-like receptor 4 signaling in diabetic nephropathy

Takashige Kuwabara, Kiyoshi Mori, Masashi Mukoyama, Masato Kasahara, Hideki Yokoi, Kazuwa Nakao

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Abstract

Dyslipidemia is an independent risk factor for the development and progression of diabetic nephropathy (DN). In this review, we summarize mouse models with both diabetes and dyslipidemia, and their associated complications. We then discuss molecules potentially involved in deterioration of DN by dyslipidemia. We focus especially upon toll-like receptor 4 (TLR4) and one of its endogenous ligands, myeloid-related protein 8 (MRP8 or S100A8), since we have found that their mRNA levels are commonly increased in glomeruli of type 1 (streptozotocin [STZ]-induced) and type 2 (A-ZIPF-1 lipotrophic) diabetic mice. Gene expression of MRP8 and Tlr4 is further upregulated during worsening of STZ-induced DN by a high fat diet (HFD). Moreover, these HFD-induced changes are accompanied by enhanced gene expression of CCAAT element binding protein β and phosphorylation of c-Jun N-terminal kinase in the kidney, which have also been reported in pancreatic β cells under diabetic-hyperlipidemic conditions. Effects of a HFD upon DN are cancelled in Tlr4 knockout mice. Macrophages are the predominant source of MRP8 in glomeruli. In cultured macrophages, combinatorial treatment with high glucose and palmitate amplifies MRP8 expression in a Tlr4-dependent manner, and recombinant MRP8 protein markedly increases gene expression of the inflammatory cytokines interleukin- β and tumor necrosis factor α . Here, we propose 'macrophage-mediated glucolipototoxicity' via activation of MRP8/TLR4 signaling as a novel mechanism of pathophysiology for DN.

Japanese Society of Nephrology

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Introduction

Diabetic-hyperlipidemic mouse models

Molecules involved in glucolipototoxicity in the kidney and pancreatic β cells

The role of M1 and M2 macrophages in DN with glucolipototoxicity

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The screenshot shows the website of the Japanese Society of Nephrology (一般社団法人日本腎臓学会). The page is in English. The navigation menu includes "HOME", "一般の方へ", "学生・研修医向け", "医療従事者向け", and "会員向け". The main content area is titled "Journal" and includes a breadcrumb "HOME >> Journal". Below this, there is a section for "CEN (Clinical and Experimental Nephrology)" with a description of the journal. A sidebar on the left contains a menu with "Journal" highlighted in a red box. The main content area has a "投稿・査読" section with links for "投稿・査読はこちら [外部リンク]" and "Online 操作マニュアル". Below that is a "閲覧・検索" section with instructions on how to use the search function. At the bottom, there are three links: "→会員の方はこちら (ユーザー名、パスワードの入力が必要です)" (highlighted in a red box), "→会員以外の方はこちら", and "→会員の方はこちら".