Abstract

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Western Diet Triggers NLRP3-Dependent Innate Immune Reprogramming.

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OBJECTIVE: Long-term epigenetic reprogramming of innate immune cells in response to microbes, also termed "trained immunity," causes prolonged altered cellular functionality to protect from secondary infections. Here, we investigated whether sterile triggers of inflammation induce trained immunity and thereby influence innate immune responses.

METHODS AND RESULTS: Western diet (WD) feeding of $Ldlr^{-/-}$ mice induced systemic inflammation, which was undetectable in serum soon after mice were shifted back to a chow diet (CD). In contrast, myeloid cell responses toward innate stimuli remained broadly augmented. WD-induced transcriptomic and epigenomic reprogramming of myeloid progenitor cells led to increased proliferation and enhanced innate immune responses. Quantitative trait locus (QTL) analysis in human monocytes trained with oxidized low-density lipoprotein (oxLDL) and stimulated with lipopolysaccharide (LPS) suggested inflammasome-mediated trained immunity. Consistently, $Nlrp3^{-/-}$/$Ldlr^{-/-}$ mice lacked WD-induced systemic inflammation, myeloid progenitor proliferation, and reprogramming.

CONCLUSION: Hence, NLRP3 mediates trained immunity following WD and could thereby mediate the potentially deleterious effects of trained immunity in inflammatory diseases.

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