A Western Diet, but Not a High-Fat and Low-Sugar Diet, Predisposes Mice to Enhanced Susceptibility to Imiquimod-Induced Psoriasiform Dermatitis

TO THE EDITOR
Psoriasis is a disease with systemic inflammation and accompanied by multiple comorbidities, including metabolic syndrome and obesity (Hwang et al., 2017; Tsai et al., 2017; Yu et al., 2017). Obesity is often observed in patients with psoriasis and may precede development of psoriasis (Debbaneh et al., 2014). Western diet (WD) plays a crucial role in the development of obesity in Western countries and is characterized by elevated amounts of fat and sugars, especially simple sugars such as sucrose (Jena et al., 2017). Recent research has revealed that, in a murine model, WD triggers systemic inflammation via the NLRP3 inflammasome and subsequent production of pro-inflammatory cytokines, such as IL-1β (Christ et al., 2018). On the other hand, a high-fat diet (HFD) without excessive sugars is often used to establish murine models of obesity. Herein, we established two models of obesity by feeding mice with a WD or HFD. The WD is not only rich in fat but also has a high sucrose content, replicating the type of diet in the Western world that contributes to obesity. The HFD obtains 60% of calories from fat and has a sucrose content that is similar to regular mouse chow. We compared these two kinds of diet-induced obese mice with lean mice on control diets in terms of susceptibility to imiquimod (IMQ)-induced psoriasiform dermatitis (PsD). Animal protocols were approved by the Institutional Animal Care and Use Committee at the University of California, Davis. Of interest, mice on HFD gained more weight than mice on WD by week 7 of feeding and sustained this increased body mass over the course of the experiment (Figure 1a, b). The measurement of ear thickness change following exposure to topical IMQ (Cochez et al., 2017; Yu et al., 2019) or intradermal IL-23 (Mabuchi et al., 2011) is a standard method to assess the extent of PsD. Although mice fed with HFD had the greatest weight gain, mice fed with WD for 12 or 16 weeks had significantly more ear thickness change than mice fed with control diet, HFD, and low-fat diet after a 5-day IMQ treatment course ($P < 0.0001$) (Figure 1c, d). There was no difference in ear thickness change between HFD- and low-fat diet–fed mice on day 5. Thus, mice on WD, but not HFD, had enhanced susceptibility to IMQ-induced PsD 3–4 months after sustained feeding, despite greater weight gain in HFD-fed mice. WD-fed mice showed consistently greater epidermal hyperplasia than the other three dietary groups (Figure 1e, f). Because neutrophils are a characteristic feature of psoriatic lesions and may play a key pathogenic role in psoriasis, we quantified neutrophil abscess formation as well as neutrophil chemoattractants in the four dietary groups. While there was no difference in Cxcl1 expression, WD-fed mice had higher expression of Cxcl2 than HFD-fed mice after 5-day IMQ treatment (Figure 1g, h). WD-fed mice had the highest expression level of neutrophil marker Ly6g mRNA and the highest density of Munro microabscess (Figure 1i, j). Consistent with reverse transcriptase PCR findings, more Gr1+ cells were observed in IMQ-treated WD-fed mice than other groups (Figure 1k, l). Expression levels of Ly6c mRNA were not different among four dietary groups, which indicates higher expression of Gr1 in WD-fed mice results from higher expression of Ly6g but not Ly6c (Supplementary Figure 1 online). Therefore, compared to the other three dietary groups, WD-fed mice had increased epidermal hyperplasia in response to IMQ, as well enhanced expression of a neutrophil chemoattractant, which may explain the histologic appearance of IMQ-treated skin in the WD-fed mice. Our previous research has indicated CCR6+ T helper type 17 cells and γδ T cells secrete IL-17A in murine psoriasiform models (Mabuchi et al., 2013). Because IL-17A is a key mediator of neutrophilic inflammatory states, we postulated that IL-17A may help explain the enhanced neutrophilic infiltration observed in WD-fed mice after IMQ treatment. As anticipated, IMQ induced higher gene expression of IL-17a in all four dietary groups (Figure 2a). To determine whether the different diets could alter baseline expression of inflammatory cytokines in skin, we next assessed their expression in vehicle-treated ears, which reflect expression of these cytokines in the absence of IMQ stimulation. Strikingly, WD induced a 45-fold increase of IL-17a compared with control diet, while HFD induced only a 20-fold increase (WD vs. HFD, respectively).

Abbreviations: HFD, high-fat diet; IMQ, imiquimod; PsD, psoriasiform dermatitis; WD, Western diet

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Gene expression levels of IL-22 and IL-23, both key psoriasis-related cytokines, were highly elevated in IMQ-treated skin of the various dietary groups as expected, but were not different in the vehicle-treated ears of HFD and WD mice compared to control counterparts (Figure 2b, c). Thus, WD mice show a specific trend
toward elevated IL-17a, but not IL-22/23, in the skin, potentially explaining the enhanced reactivity to IMQ. Of note, WD-fed mice had the highest expression level of Nlrp3 and pro-inflammatory cytokine IL-1b genes among four dietary groups after a 5-day course of IMQ. As compared with HFD-fed mice, WD-fed mice had higher mRNA levels of Nlrp3 and IL-1b than HFD-fed mice. (f) There was no difference in the expression of Tnf-a among four dietary groups. CD, control diet; HFD, high-fat diet; IMQ, imiquimod; LFD, low-fat diet; NS, no statistical significance; WD, Western diet. *P < 0.05, **P < 0.01.

The mechanisms of how sugar exacerbates psoriasis are likely multifactorial. Reports suggest that WD triggers systemic inflammation via the NLRP3/IL-1β activation (Christ et al., 2018), potentially with subsequent induction of neutrophil chemottractants, such as CXCL1 (Amaral et al., 2012). Another possibility is that sugar intake could change gut and skin microbiota and modify the cutaneous immune microenvironment to potentiate skin to psoriasisform dermatitis. For example, one study shows that WD induces a shift in gut microbiota composition and enhances susceptibility to E. coli infection and intestinal inflammation (Agus et al., 2016). Dietary components not only change gut microbiota, but influence cutaneous inflammation via the gut–skin axis (Maguire and Maguire, 2017; O’Neill et al., 2016). It is intriguing that CXCL2, but not CXCL1, is elevated in WD-fed mice. Although CXCL1 and CXCL2 do regulate NLRP3 inflammasome activation via the same G protein–coupled receptor CXCR2 (Boro and Balaji, 2017), the literature has indicated that CXCL1 and CXCL2 do not necessarily contribute equally (Ritzman et al., 2010), suggesting that non-parallel induction of one or the other may occur in some situation.

The fact that HFD-fed mice have more body weight gain but less inflammation in response to IMQ than WD-fed mice strongly suggests obesity alone is not sufficient to promote PsD in the skin. Intriguingly, a recent study indicated that a high-dietary-fat diet exacerbates psoriatic skin inflammation independent of obesity (Herbert et al., 2018). Another study, using different chow recipes, also
Disinhibition of Touch-Evoked Itch in a Mouse Model of Psoriasis


TO THE EDITOR

Alloknesis, itch due to light mechanical stimulation, is frequently associated with dry skin and inflammatory skin disorders (e.g., atopic dermatitis, psoriasis). Recent studies have shown that mechanical itch is

Abbreviations: IMQ, imiquimod; LTMR, low-threshold mechanoreceptors; NFH, neuroligation; QX-314, N-ethyl-lidocaine; TLR5, toll-like receptor 5; VH, vehicle

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