MicroRNA expression profiles differentiate chronic pain condition subtypes

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Chronic pain is a significant health care problem, ineffectively treated because of its unclear etiology and heterogeneous clinical presentation. Emerging evidence demonstrates that microRNAs (miRNAs) regulate the expression of pain-relevant genes, yet little is known about their role in chronic pain. Here, we evaluate the relationship among pain, psychological characteristics, plasma cytokines, and whole blood miRNAs in 22 healthy controls (HCs); 33 subjects with chronic pelvic pain (vestibulodynia, VBD); and 23 subjects with VBD and irritable bowel syndrome (VBD + IBS). VBD subjects were similar to HCs in self-reported pain, psychological profiles, and remote bodily pain. VBD + IBS subjects reported decreased health and function; and an increase in headaches, somatization, and remote bodily pain. Furthermore, VBD subjects exhibited a balance in proinflammatory and anti-inflammatory cytokines, whereas VBD + IBS subjects failed to exhibit a compensatory increase in anti-inflammatory cytokines. VBD subjects differed from controls in expression of 10 miRNAs of predicted importance for pain and estrogen signaling. VBD + IBS subjects differed from controls in expression of 11 miRNAs of predicted importance for pain, cell physiology, and insulin signaling. miRNA expression was correlated with pain-relevant phenotypes and cytokine levels. These results suggest that miRNAs represent a valuable tool for differentiating VBD subtypes (localized pain with apparent peripheral neurosensory disruption vs widespread pain with a central sensory contribution) that may require different treatment approaches. (Translational Research 2015;166:706–720)

Abbreviations: CCPC = complex chronic pain condition; CNS = central nervous system; FM = fibromyalgia; HC = healthy controls; IBS = irritable bowel syndrome; IL-1ra = interleukin 1 receptor antagonist; IL-8 = interleukin 8; miRNAs = microRNAs; TMD = temporomandibular disorder; TMJ = temporomandibular joint; VBD = vestibulodynia

INTRODUCTION

Vestibulodynia (VBD) is a complex chronic pain condition (CCPC), characterized by entry dyspareunia, tenderness to touch, and the presence of erythema on the vulvar vestibule, which affects 10%–15% of women in the United States.[1,2] VBD often co-occurs with other CCPCs including irritable bowel syndrome (IBS; 35%),[3] temporomandibular disorder (TMD; 78%),[1] and fibromyalgia (FM; 17%).[3] VBD and related CCPCs represent a significant health care

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AT A GLANCE COMMENTARY

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Background

Chronic pain conditions are a debilitating and strikingly prevalent class of disorders that affect more individuals than heart disease, stroke, diabetes, and cancer combined. Vestibulodynia (VBD) is a common chronic pain condition that affects 10% of women in the United States and is characterized by pain at the vulvar vestibule. VBD often co-occurs with other chronic pain conditions, characterized by pain at nearby or distinct anatomic sites. The present study elucidates novel clinical features and biological pathways unique to women with VBD alone and to those with VBD plus co-occurring pain conditions.

Translational Significance

Collectively, the implications of these data extend beyond the field of pelvic pain. These results elucidate chronic pain condition subtypes with unique etiologic mechanisms and suggest the utility of microRNAs for individual-based diagnosis and treatment. Furthermore, the approach of stratifying and treating patient groups based on molecular correlates is novel and has broad implications far beyond the field of pain.

problem, together affecting up to 1 billion adults worldwide.[4] Current treatment regimens remain ineffective because of the conditions' uncertain etiology and heterogeneous clinical manifestation.[1] To understand the nature of these complex conditions and improve standards of care, the identification of unique biological signatures and pathways that map onto distinguishing clinical features is required.

Although clinical manifestations are heterogeneous, VBD and related CCPCs are associated with a state of pain amplification, psychological distress, and enhanced inflammation.[5] In VBD, pain is localized to the pelvis, possibly because of altered permeability or cellular composition of the mucosa.[1] Women with VBD demonstrate higher levels of anxiety and somatization as well as enhanced production of proinflammatory cytokines.[2] Compared with individuals with 1 CCPC, those with co-occurring CCPCs exhibit increased psychological distress[1] and imbalances in proinflammatory and anti-inflammatory mediators possibly indicative of abnormalities in central pain processing.[6]

MicroRNAs (miRNAs) represent biological determinants of pain, mood, and inflammation. miRNAs are small, noncoding pieces of RNA that control gene expression by inhibiting protein translation or degrading downstream target mRNAs.[7] Aberrant miRNA profiles have been associated with several animal models of pain and inflammation as well as painful conditions in humans.[8] Furthermore, miRNA profiling represents a novel and clinically relevant approach for patient stratification of pain-related conditions.[9] Emerging evidence also suggests a role for miRNAs in psychological conditions such as depression and anxiety.[10] Lastly, miRNAs regulate genes involved in activation of immune cells and secretion of inflammatory cytokines.[11] This suggests that miRNAs are key contributors to the pain amplification, psychological distress, and enhanced inflammation characteristic of CCPCs such as VBD.

We elucidate novel clinical features and biological pathways unique to women with VBD and to those with VBD plus a commonly co-occurring CCPC, IBS (VBD + IBS). Specifically, those with VBD have pain localized to the pelvis, normal self-reported pain and psychological profiles, increased levels of proinflammatory and anti-inflammatory cytokines, and dysregulation of miRNAs predicted to be involved in pain processing and estrogen signaling. Those with VBD + IBS have greater pain sensitivity at remote bodily sites, enhanced self-reported pain and somatization, imbalanced proinflammatory and anti-inflammatory responses, and dysregulation of miRNAs predicted to be involved in pain processing, cellular physiology, and central sensory pathways. Collectively, these results suggest miRNA profiles may be useful for understanding the shared and unique mechanisms of localized vs widespread pain conditions.

MATERIALS AND METHODS

Subject consent and enrollment. All subjects were enrolled after giving informed consent as approved by the Biomedical Institutional Review Board of the University of North Carolina at Chapel Hill (UNC).

Inclusion and exclusion criteria. This study used data from 78 women (33 VBD, 23 VBD + IBS, and 22 healthy controls [HCs]). Subjects in VBD and VBD + IBS groups were recruited at the UNC Pelvic Pain Clinic and subjects in the HC group were recruited through fliers placed on campus and in the local community between August 2008 and August 2010. Sample sizes were based on prior miRNA studies.[9,12-14] Preliminary eligibility assessment of interested subjects was conducted via a phone interview. Subjects were excluded for a positive response to any