Chapter 1

Introductory Chapter: A Challenge to the Concept that Inflammation Plays a Prominent Pathogenic Role in Fibromyalgia

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1. Introduction

Among the chapters in this monograph are those that examine the treatment of fibromyalgia syndrome (FMS) using nonpharmacologic natural products and other relatively novel agents [1–3]. Although the modes of therapy described are diverse, a role for disordered immune mechanisms is implicit in each of the three chapters. These include reference to sulfur springs considered to inhibit interleukin-2 and interferon-gamma [1], introductory explanations of FMS pathogenesis that invokes inflammatory dysfunction [2], and mention of inflammatory cytokine production associated with autonomic nervous system dysfunction-stimulated microglial and astrocyte cell activation [3]. The discussion in the fourth chapter about the impact of FMS on the evaluation of inflammatory diseases assumes the opposite that clinically significant inflammation is not a feature of FMS [4].

2. Case (should have been previously) closed

Face validity favoring a major pathogenic role for cytokine-mediated inflammation in FMS has been addressed in the past. Although initial reports of intermuscular fibrous tissue inflammation by Stockman led Gowers to name the condition "fibrositis," [5, 6], contemporary light and magnetic resonance imaging histological reports showed no evidence for peripheral muscle inflammation [7, 8]. These data should have closed the book on inflammation as a prominent etiopathogenic mechanism in FMS. Then along came inflammatory mediators.

In some contemporary reviews of FMS pathogenesis, inflammation is referenced in passing, as it is in these three chapters [9]. Whether this is done for "completeness," after all, FMS is

often misclassified as a "connective tissue disease" (a misnomer), most of which are inflammatory in nature, or that such reference adds a sort of "scientific patina" to the discussion is unclear.

This review examines the validity of the concept that cytokine- and chemokine-driven inflammation is relevant to the pathogenesis of FMS.

3. Background

At least three observations have been used to provide circumstantial or hypothesis-generating evidence to advance a role for inflammatory pathogenesis:

1. The symptoms and signs of "sickness behavior" observed in FMS can be experimentally induced by inflammatory cytokines [10].
2. Similar alteration of the hypothalamic–pituitary axis and autonomic nervous system observed in FMS has been etiopathogenically linked to elevated inflammatory cytokines, including interleukin-1 (IL-1), in a variety of clinical settings other than FMS [11–14].
3. Symptoms of disordered sleep, hyperalgesia, and cognitive dysfunction much like FMS were observed when patients with renal cell carcinoma were treated with interleukin-2 lymphokine-activated killer (IL-2 LAK) cell therapy and when chronic hepatitis patients were treated with interferon alpha [15].

4. Experimental evidence for cytokine/chemokine pathogenesis

1. Previous inconsistent reports have demonstrated that C-reactive protein (CRP) can be marginally higher in FMS subjects than in parallel healthy controls [16]. In this analysis, however, serum inflammatory cytokines were not higher than in healthy controls.
2. Inconsistent elevation of a variety of serum cytokines has, however, been observed in some studies [16–24]. In a meta-analysis of 25 FMS studies, 1255 FMS, and 800 healthy controls (HC), interleukin-1 receptor antagonist (IL-1ra), interleukin-6 (IL-6), and interleukin-8 (IL-8) were the most likely inflammatory cytokines to be elevated [25].

Three integrated reviews, although acknowledging discrepancies in the literature, attempted to associate cytokine abnormalities with core FMS symptoms [26–28]. The first concluded, "There are discrepant findings related to whether pro-inflammatory and anti-inflammatory cytokines are elevated or reduced in persons with FMS and whether they correlate with core symptoms." [26]. The second [27] critiqued one of the more persuasive analysis, "….. may have cytokine driven abnormalities to explain their pain…IL-1ra and IL-6 were significantly higher after stimulating PBMC of FMS patients compared to controls [29]." The results of this study were not corroborated in a second study [24].

The third review of 12 separate analyses reported increased inflammatory cytokines IL-1ra, IL-6, and IL-8, and anti-inflammatory interleukin-10 (IL-10) or low anti-inflammatory interleukin-4 (IL-4) and IL-10 [24]. Among the inflammatory chemokines also linked to signs and symptoms, monocyte chemoattractant protein-1 (MCP-1), eotaxin among others, were elevated.

Two potentially innovative separate controlled analyses described cytokine and chemokine concentrations in the supernatant after mitogen stimulation of cultured monocytes, using a logistical regression model to achieve statistically determined weighting for each chemokine and cytokine, and offered this score as diagnostic test for FMS [30, 31]. Of interest, the inflammatory cytokines and chemokines including IL-6 were lower in concentration compared to healthy controls or individuals with autoimmune disease. These findings suggest increased damping control of inflammation in FMS. The authors of both these studies, however, failed to determine the prevalence of depression or analyze its potential effects on cytokine concentrations.

Among the most novel analyses was a report of elevation of intrathecal IL-8 derived from glia cells supporting the hypothesis that FMS symptoms might be mediated by glial cell activation through sympathetic nervous system mechanisms [32].

In summary, in individuals with FMS, peripheral blood IL-6, IL-1ra, and IL-8 concentrations may be a bit higher and IL-4 and IL-10 lower, and IL-8 may be relatively higher in the cerebral spinal fluid than in healthy controls. Inflammatory chemokines may also be higher than in healthy control patients.

5. Depression and inflammation

Depression and FMS are very often comorbid and show a bidirectional association [19, 33–38]. The prevalence of depression in FMS has been estimated to range from 20 to 80% in a detailed review [39]. Furthermore, the severity of comorbid depression correlates with FMS severity measures [40–42]. We have reported that depression, with a 73% prevalence, correlated better with core FMS symptoms than did any other variable in a cohort of 305 FMS patients [43].

As in FMS, similar mild elevation of CRP and inflammatory cytokines and chemokines have been demonstrated in depressed individuals in controlled analyses [44–53]. Many primary analyses of FMS inflammation [15, 30, 31, 54–56] and reviews [23, 28], however, failed to control for depression. This is an unfortunate omission.

Maes and colleagues evaluated the serum concentrations of inflammatory cytokines in relationship to depression among 21 FMS patients compared to 33 healthy controls [57].

Serum soluble gp130, an important inflammatory cytokine signal transducer, and a soluble interleukin-6 receptor, Il-1 ra, were significantly higher in FMS patients with a Hamilton Depression Rating Scale score >16 than in FMS patients with scores of 16 or lower or in healthy controls. In the opinion of the Menzies' integrated review, which included the Maes analysis, higher inflammatory cytokines in FMS, including IL6, were related to the degree of depression, although inconsistencies were common [26].

Of interest, higher body mass index partially explained cytokine differences as has been shown in depression [18, 52]. Therefore, inflammation in FMS, measured as higher serum concentrations of cytokines and chemokines, is multifactorial and not necessarily due solely to FMS pathophysiology.

Serum inflammatory cytokine concentrations correlate with the degree of depression and fall with effective treatment of depression [58]. Not surprisingly, inflammatory cytokine concentrations have also been shown to correlate with pain symptoms in primary depression alone [59].

This phenomenon even occurs when the treatment is nonpharmacological, suggesting an intrinsic etiopathophysiologic relationship of inflammatory cytokines with depression [46]. This analysis also demonstrated that despite a significant fall of cytokine concentration from baseline, the CRP was not significantly lower.

In summary, these two analyses demonstrate a pain symptom signature integral to depression and that cytokines, while slightly higher in depression than in healthy controls, are in fact trivial with respect to overall inflammation measured as CRP.

6. Different process mechanisms: RA versus FMS/depression

6.1. RA

In rheumatoid arthritis (RA) comorbid FMS is associated with disproportionately higher values for the subjective components, patient global assessment (PtGA), and tender joint count (TJC), which in turn inflate the disease activity score (DAS). This phenomenon is largely mediated by higher patient assessed pain, fatigue, and especially poor mood, and variables that define the criterion, distress, and the etiopathogenesis of FMS [60–64]. As a potential explanation, depression alone can disproportionately increase pain sensitivity, the tender joint count (TJC), and a patient's sense of wellbeing, such as PtGA in RA [19, 65]. Higher subjective signs and symptoms then inflate the DAS. It is important to note that concomitant FMS and depression in RA are not associated with obvious, clinically significant increases of CRP or erythrocyte sedimentation rate [42, 62, 65].

Differential response to the treatment of the so-called subjective versus objective variables is a hallmark of comorbid FMS and/or depression in RA. In a prospective analysis of 668 RA patients, 18% with comorbid FMS had higher DAS and Health Assessment Disability Index at baseline compared to patients without FMS [66]. The TJC and PtGA were significantly higher, but the objective factors, ESR, and swollen joint count (SJC) were significantly lower in patients with FMS compared to patients with RA alone. Achievement of low disease activity and remission were significantly less likely in the comorbid FMS cohort. Others have confirmed these observations [67].

A very instructive, early, placebo-controlled trial showed that the pain of FMS did not respond to the treatment with prednisone 15 mg/day [68]. So too, unlike dose-related reduction of objective signs in RA such as the swollen joint count (SJC) and CRP, FMS-related inflated subjective signs and symptoms are resistant to aggressive anti-immune, anti-inflammatory

RA treatment [69–71]. In fact, a treatment response resulting in remission in RA comorbid with FMS should not be expected because the higher, poorly responsive PtGA and TJC are not due to RA biological disease activity, but in fact to poorly responsive noninflammatory FMS central pain mechanisms [69].

7. Differential magnitude of inflammatory response

Mean CRP values, although reported elevated in some FMS populations compared to control populations, are still within the range of normal CRP [72]. Given this observation, it is both instructive and necessary to consider whether cytokines follow this same pattern.

7.1. Rewrite cytokine section

In RA, serum concentrations of IL-6 measured by enzyme immunoassay (ELISA) [73] in >900 patients demonstrated mean ~ 43 pg/ml, for all, and ~54–84 pg/ml for those with active disease [55]. In another population of 66 RA patients, using a similar assay, IL-6 levels declined to 22.5 pg/ml in low disease activity [74].

Contrast these serum levels with serum levels in depression and FMS. Using a different more sensitive ELISA assay, Grosse reported mean IL-6 serum concentration of 1.17 ± 2.59 for 214 patients with major depression disorder (MDD) and 0.66 ± 1.94 for healthy controls (HC) [50]. In another analysis of 64 MDD patients and 80 healthy controls, IL-6 levels were reported statistically higher in depression than in controls, 1.39 ± 0.35 versus 0.45 ± 0.28 pg/ml using yet another ELISA [47].

These same comparatively low serum levels were reported in FMS, with IL-6 in the range of 16 pg/ml in FMS and 1 pg/ml in healthy controls using yet another ELISA assay [75]. Although higher than HCs, the levels are very low when compared to those in RA.

This discussion apparently shows that inflammatory cytokines, even when relatively elevated in FMS, are much lower than in mildly active RA. If this is true, then the elevations in FMS may not be sufficiently high to initiate clinical signs or symptoms. Unfortunately, as can be seen, diverse assays that produce diverse serum and cellular concentrations and the lack of control for diurnal variation make precise comparisons between diseases difficult.

Fortunately, two papers do allow comparison. The authors of both studies used very similar ELISA methods. In 16 RA patients with varying disease activity, overnight IL-6 values ranged from a mean of ~40 pg/ml at 11 PM to a peak of ~60 at 8 AM with large individual variations [76].

In FMS, although the mean values for IL-6 were statistically significantly higher in FMS patients than in healthy controls at night (2.94 versus 2.14 pg/ml), these serum concentrations were at least 10 times lower in FMS than in RA [56]. Are these meager elevations of IL-6, ~0.80 pg/ml in FMS compared to HCs, sufficiently high enough to explain clinical differences?

Let us postulate that mildly elevated cytokines in the CNS such as IL-6 and IL-8 [32] produced by microglial and/or astrocyte cells are sufficient to interfere with processing and produce

centrally mediated pain. We are still left with the lack of clinical response to moderate daily prednisone and even more aggressive antirheumatic, anti-inflammatory treatments which have been shown to reduce inflammation due to cytokines [67, 68, 71, 77].

There is little question that FMS does associate with mild cytokine change, such as reduced diurnal variation of IL-6 compared to healthy individuals [56]. Forensic objectivity, however, would seem to indicate that the described modest changes in inflammatory mediators, whether primary or secondary, do not seem sufficient to be responsible for clinically relevant FMS symptoms. Furthermore, in some very legitimate contemporary hypotheses of FMS etiopathogenesis, there is no role for chronic cytokine-mediated processes [78, 79].

8. Conclusions

The key points from this discussion are:

1. Although a minority of studies found CRP elevated in FMS compared to healthy controls, the mean high value was still within the normal range.
2. Depression, which is very often comorbid with FMS, was not well controlled in many cytokine/chemokine analyses. When it was, it was shown to significantly contribute to higher cytokine values.
3. Fibromyalgia symptoms, whether as the primary diagnosis or as comorbid in RA, do not respond to anti-inflammatory, anti-immune therapy.
4. Both stimulated and unstimulated cytokine and chemokine studies have employed a variety of methods of measurements that make cytokine levels difficult to analyze between diseases. A few comparisons have shown relatively trivial values in FMS compared to proven inflammatory disease such as RA.

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