The Physiological Role of Tumor Necrosis Factor in Human Immunity and Its Potential Implications in Spinal Manipulative Therapy: A Narrative Literature Review

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ABSTRACT

Objective: Although tumor necrosis factor (TNF) is a well-known inflammatory cytokine in the pathological development of various human diseases, its physiological roles are not widely understood nor appreciated. The molecular mechanisms underlying spinal manipulation therapy (SMT) remain elusive. The relationship between TNF and SMT is unclear. Thus, we performed this literature review to better understand TNF physiology and its potential relationship with SMT, and we propose a novel mechanism by which SMT may achieve clinical benefits by using certain beneficial features of TNF.

Methods: We searched several databases for relevant articles published between 1975 and 2015 and then reexamined the studies from current immunophysiological perspectives.

Results: The history and recent progresses in TNF physiology research were explored. Conflicting reports on the relationship between TNF and SMT were identified. Based on the newly discovered interaction between TNF and regulatory T cells, we proposed a putative biphasic TNF response to SMT, which may resolve the conflicts in the reported observations and interpretations.

Conclusion: The current literature about TNF informed our discussion of new physiological roles for TNF, which may help to better understand the physiological effects of SMT. (J Chiropr Med 2016;15:190-196)

Key Indexing Terms: Tumor necrosis factor; Manipulation spinal; T-lymphocytes regulatory

INTRODUCTION

Tumor necrosis factor (TNF), also known as *TNF α* , *cachexin*, or *cachectin*, is an inflammatory cytokine involved in the pathology of numerous diseases. A recent article reported serious adverse effects during long-term anti-TNF therapy,¹ which may indicate its beneficial functions at normal physiological levels. These beneficial physiological functions are unfamiliar to us in the complementary and

alternative medicine (CAM) field. We are wondering whether this is an isolated report or an important issue widely underappreciated. Thus, a better understanding of TNF physiology and its current research progresses is warranted.

Spinal manipulative therapy (SMT) is a clinical approach widely used by CAM practitioners, such as doctors of chiropractic, osteopathic physicians, physical therapists, and some traditional Chinese medicine specialists, for maintaining general muscular skeleton health or/and alleviating pain.²⁻⁶ Current SMT theories are based on an earlier understanding of spine anatomy and neurophysiology.^{7,8} The human body functions through various specialized cells working in concert. These cellular activities are controlled and coordinated at a variety of biological levels that include molecules acting as mediators. The current research has not examined the manner in which SMT may affect molecular controlling mechanisms.

Spinal manipulative therapy is thought to have a certain relationship with cytokines such as TNF. Brennan et al⁹ first reported a stimulatory effect of SMT on TNF production in healthy human subjects. However, a

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subsequent study by Teodorczyk-Injeyan et al¹⁰ reported that SMT inhibited TNF synthesis in humans. If both results were true, one would need to reconcile those conflicting reports and provide a reasonable explanation based on sound scientific background. In addition, as SMT is a physiological maneuver, it seems more likely that SMT would be associated with TNF at normal physiological levels.

To address these issues, the purpose of this study is to review the literature regarding the physiological roles of TNF and its potential relationship with SMT. In this narrative review, we summarize our findings and propose a novel mechanism by which SMT may achieve clinical benefits by using certain beneficial features of TNF.

METHODS

We searched the PubMed, Cinahl, ICL, Mantis, and PEDro databases using a time frame from 1975 to 2015. The year 1975 was chosen because that was the year TNF was discovered.¹¹ We initially searched for articles on normal TNF physiology, which are much less common than articles on TNF pathology. We used the following search strategy: (“TNF” or “TNF α ” or “cachexin” or “cachectin”) and (“physiology” or “beneficial”). Next, we focused on the relationship between SMT and TNF by using the following search strategy: (“TNF” or “TNF α ” or “cachexin” or “cachectin”) and (“chiropractic adjustment” or “spinal manipulation” or “osteopathic manipulation” or “manipulative treatment” or “spinal adjustment”). After screening by title, abstract, and full text, we obtained a list of pertinent literature. We then searched the article bibliographies to identify additional studies that were added to the list.

Fig 1. Recent research resurgence on the physiological roles of TNF. Publications on TNF physiology during the indicated time periods were counted. Then, the annualized rate for each period was calculated and drawn in the bar graph.

RESULTS

A Recent Resurgence of Research Interest on Normal TNF Physiology

Compared with thousands of articles published on the pathological roles of TNF in numerous diseases and disease models, very few studied normal TNF physiology. TNF was first discovered in 1975 by Carswell et al.¹¹ Its purification in 1980^{12–14} triggered an initial surge of research interest in its physiology with a total of 86 articles published by the end of 1985 (ie, an annual rate of 12.7 articles; Fig 1). However, since Beutler and Cerami¹⁵ proposed a role for TNF in shock and inflammation in 1986, the pathophysiology of TNF has gradually drawn far more attention than its normal physiology. From 1986 to 1991, we found only 9 articles reporting the normal physiological effects of TNF (ie, an annual rate of 1.8 articles during that period). Since 1991, almost all literature related to TNF has examined its pathological roles. Anti-TNF therapy was proposed¹⁶ and is now used to treat arthritis, inflammatory bowel disease, and psoriasis.^{17–20} However, several recent articles reported serious tumor and infection adverse effects in anti-TNF therapy during long-term, large-scale clinical trials.^{1,21,22} Since 2011, 16 articles have reported the beneficial effects of normal physiological TNF (ie, an annual rate of 4 articles on the topic). In contrast to the near silence on normal TNF physiology research from 1992 to 2010, the current activity represents a resurgence of interest on this topic (Fig 1). Two recent articles highlighted the importance of normal physiological TNF. Johansson et al²³ (2012) found that “low-dose TNF α promotes both vessel remodeling and antitumor immune responses” in mice. Chen et al²⁴ (2007) discovered that physiological TNF triggers a negative feedback from regulatory T cells (Tregs) to inhibit its own synthesis and thus controls final TNF level. This finding has led to a recent speculation for physiological TNF in anti-inflammation,²⁵ as Tregs are the key to contain inflammation physiologically.²⁶

The Confused Relationship Between TNF and SMT

Regarding the relationship between TNF and SMT, we found 3 articles: (1) Brennan et al⁹ (1992) reported a 61% increase of endotoxin-induced TNF in human monocytes isolated from healthy individuals treated with upper thoracic SMT as compared with the controls. The authors suggested that this phenomenon might indicate a tissue damage effect of SMT and that TNF increase could be used as a specific biomarker for identifying a physiologically effective SMT. (2) Teodorczyk-Injeyan et al¹⁰ (2006) reported that a similar upper thoracic SMT actually produced an up to 37% reduction of lipopolysaccharide (LPS)-induced TNF in monocytes isolated from healthy individuals. The authors suggested that this was direct evidence for an anti-inflammatory effect of SMT. (3) Ormos et al²⁷ (2009) reported that manipulative therapy (no

specifications) achieved a 50% to 55% reduction of high TNF levels in blood samples from headache patients.

The first 2 studies on this topic appeared contradictory to each other, even though very similar SMT techniques and similar outcome methods were used.^{9,10} Close examination revealed that the investigators applied different LPS incubation times. Brennan et al incubated the monocytes with endotoxin/LPS for 2 hours, whereas Teodorczyk-Injeyan et al incubated the monocytes for 24 hours. This time difference may be critical to understand the apparent conflict between these studies.

DISCUSSION

To our knowledge, this is the first attempt to understand the existing literature on the physiological roles of TNF and its potential relationship with SMT. The literature presents a complicated picture. Thus, reexamining the relevant literature from a new immunophysiological perspective—that normal physiological TNF may have beneficial effects on human health—might provide a clearer understanding.

The detrimental role of TNF is widely appreciated in human pathology. During the last 2 decades, TNF has been implicated in numerous diseases such as arthritis,¹⁷ Alzheimer disease,²⁸ cancer,²⁹ major depression,³⁰ septic shock,³¹ and inflammatory bowel disease.³² Therefore, anti-TNF therapy has been used in clinical practice.^{17–20} TNF also plays an essential beneficial role in a variety of physiological functions including immune surveillance, sleep regulation, synaptic scaling, and neurogenesis.^{33–38} TNF was initially recognized for its ability to kill tumor cells without harming normal cells.¹¹ In addition to confirming this antitumor capacity,^{12–14} early studies also reported that TNF was essential in anti-infection.^{35,39} TNF is chiefly produced by macrophages during acute immune reactions to kill invading foreign organisms or mutated self-cells.^{34–36,40} Macrophages subsequently present digested foreign or mutated antigen to T cells for immune memorization and further immune reactions.^{35,36} It is well known that TNF is required to activate effector T cells (Teffs) during the inflammatory process,^{41,42} which may be an essential step for TNF to achieve its “bad molecule” roles. However, researchers recently showed that TNF also stimulates a subpopulation of T cells, called *Tregs*, to proliferate. The *Tregs* then inhibit further TNF synthesis as a negative feedback.⁴³ This negative feedback mechanism ensures a controlled immune reaction that protects the body without inflammatory damages.^{24–26} With the persistent presence of foreign organisms or certain internal factors, activated macrophages continue to produce high levels of TNF that shift the balance to favor the action of Teffs, instead of *Tregs*,^{24–26} which are harmful to normal tissues and lead to a full-blown inflammation.¹⁵ It is important that we distinguish the pathological actions of chronic,

high-level TNF from the transient, small spikes of normal physiological TNF, as it will shift the balance to activate different subsets of T cells and thus cause either beneficial or harmful effects.^{33–36}

The importance of physiological TNF in human immunity recently seems to be regaining attention as researchers observed that anti-TNF therapy caused serious adverse effects in some patients (Fig 1). For example, Keystone¹ (2011) reviewed the tumor and infection adverse effects associated with long-term anti-TNF therapy. An anti-TNF therapy meta-analysis by Thompson et al²² (2011) confirmed these serious adverse effects, and this has been further supported by recent studies.^{18,20,21,44,45} In addition, decreased macrophage TNF is critical in aging-associated immunity deficiency.⁴⁶ These studies highlight the essential role of TNF in human immunophysiology. Furthermore, using TNF to kill tumor cells has been proposed in cancer treatment⁴⁷; and exciting positive results have been reported in an animal model. Johansson et al²³ (2012) found that “low-dose TNF promotes both vessel remodeling and antitumor immune responses” in mice. Although a report cast doubt on the role of TNF in neutrophil recruitment (a key component of the inflammatory process),⁴⁸ Chen et al²⁴ (2007) discovered that physiological TNF triggered a negative feedback from *Tregs* to inhibit its own synthesis and thus control the final TNF level. Researchers now appreciate the anti-inflammatory role of physiological TNF in activating and expanding *Tregs*, the central player in the negative feedback loop to suppress inflammation physiologically.^{25,26} Therefore, these recent advancements clearly demonstrate key roles for physiological TNF in immune surveillance against tumor and infectious agents, and in the physiological control against inflammation via activating *Tregs*.

How could this new knowledge help us to understand the relationship between TNF and SMT as reported in the literature? We first examined why the very similar SMT treatments produced opposite TNF effects.^{9,10,27} At first glance, these 2 studies seemed directly incompatible. The study of Brennan et al⁹ examined the difference in polymorphonuclear neutrophil activity in mixed mononuclear cells from blood samples obtained from SMT-treated human subjects; the article of Teodorczyk-Injeyan et al¹⁰ described quantifications of TNF and substance P in SMT-treated human subjects using enzyme immunoassay. Although the study of Teodorczyk-Injeyan et al involved measuring the level of substance P in serum samples, both studies shared a very similar experimental design in determining TNF level: after upper thoracic SMT, a wait time followed, then whole blood samples were obtained from study subjects, and mixed peripheral blood monocytes were pooled for cell culturing and then challenged by incubating with endotoxin/LPS, which is known to stimulate TNF production. Despite various wait times (20

minutes to 2 hours) after SMT treatment conducted by Teodorczyk-Injeyan et al, a consistent reduction of TNF production was observed in all SMT-treated subjects (Table 2 of the article of Teodorczyk-Injeyan et al), which was directly contradictory to the report of Brennan et al of rising TNF after a short waiting time (30-45 minutes).^{9,10} One could argue that the enzyme immunoassay used by Teodorczyk-Injeyan et al was more sensitive in TNF measurement than the bioactivity assay used by Brennan et al. This could make sense if there were only a degree of differences. However, the striking opposite results indicate that assay sensitivity is not a valid argument. Finally, after a close examination of these 2 studies, we found that the investigators actually applied different LPS challenging times during cell culture. Brennan et al incubated the monocytes with endotoxin/LPS for only 2 hours, whereas Teodorczyk-Injeyan et al incubated the monocytes with endotoxin/LPS for 24 hours. Could this time difference be critical to understand the apparent conflict between these studies?

The 2-hour incubation time applied by Brennan et al⁹ likely mimicked an acute immune challenge to the isolated monocytes, specifically the ability of macrophages to produce TNF. That short incubation time was insufficient for the cell-to-cell communication required to mount an integrated immune response. Thus, Brennan et al focused on acute TNF response from macrophages, an immune surveillance function. By contrast, the 24-hour incubation time applied by Teodorczyk-Injeyan et al¹⁰ produced a substantially different TNF response. The longer incubation time in this study was sufficient for the cell-to-cell communication required to mount an integrated immune response that initiates a negative feedback cycle from Tregs to macrophages, which could reasonably explain their reported reduction of TNF production. Thus, Teodorczyk-Injeyan et al focused on the integrated immune response that involves multiple cellular components. Long-term treatment with LPS may induce cell death,⁴⁹ which could selectively kill certain monocyte subpopulations, thus contributing to TNF reduction. This potential mechanism needs further investigation. Most likely, the reduced TNF synthesis reported by Teodorczyk-Injeyan et al¹⁰ was due to negative Tregs feedback triggered by the earlier, SMT-induced acute elevation of TNF. Thus, the work of Teodorczyk-Injeyan et al may actually not be in conflict with the study of Brennan et al. The authors simply studied different time points on a biphasic TNF curve in response to SMT (Fig 2). The work of Brennan et al demonstrated an SMT-enhanced response from macrophages in the short term, whereas the work of Teodorczyk-Injeyan et al demonstrated an SMT-enhanced negative feedback from Tregs in the longer term. The case report of symptomatic patients by Ormos et al²⁷ further suggests a possibility that SMT may reduce high TNF levels in inflammatory

patients by sensitizing Tregs. Future studies with adequate sample sizes and proper experimental designs will be required to settle this issue.

Based on the arguments presented above, it is possible that SMT could produce a biphasic TNF response in humans (Fig 2). Initially, SMT may trigger an enhanced TNF production by macrophages,⁹ which activate Tregs that provide a negative feedback^{24-26,43} to subsequently inhibit TNF synthesis in a late phase.¹⁰ This biphasic response may impact human health in 2 ways, depending on the individual's condition. In healthy, noninflamed individuals, SMT may boost immune surveillance via enhanced macrophage TNF production (Figs 2 and 3).^{9,35,46} This uses the beneficial feature of physiological TNF and may be one of the reasons why SMT is effective during wellness management for rather healthy individuals.⁴ In inflammatory pain conditions, the early TNF spike produced by SMT may serve as a fresh stimulus, sensitizing and activating Tregs to the chronically high level of TNF. This may therefore shift the balance from activating Tregs to Tregs and jumpstart the negative feedback mechanism to suppress TNF synthesis and improve those inflammatory conditions (Fig 3). Similarly, activation of Tregs by TNF may explain the SMT-induced reduction of other inflammatory cytokines reported in patients with low back pain.⁵⁰ However, the relationship between TNF and other SMT-associated immunoregulatory molecules⁵¹ remains to be sorted out. Studies on this topic are still limited, and it will require further research to firmly establish the relationship between physiological TNF and SMT. Particularly, it remains to be examined whether the physiological TNF spike initiated by SMT would preferentially activate Tregs as we propose here (supported by the work of Teodorczyk-Injeyan et al) or would do nothing to shift the balance between Tregs and Tregs, or possibly even activate Tregs. These different outcomes will determine the beneficial or meaningless, even harmful, impacts on human body following an SMT-TNF reaction.

Limitations and Future Studies

This review of the literature was not a systematic review because reports on these topics are limited. The limitations to this study include that there may have been articles that we missed or that we were not aware of in other search engines.

There are a plethora of studies and reports on the physiological role of TNF. However, the conflicting and confusing status on the relationship between TNF and SMT has dampened researchers' enthusiasm, with only limited output reported in the literature. In the present study, we propose a putative, testable hypothesis based on the literature but without any direct, concrete, experimental data. Therefore, more vigorous experimental studies are required to firmly establish a relationship between TNF and

Fig 2. Putative TNF biphasic response to SMT. Red arrow indicates the time to apply SMT (spinal manipulation). Green arrow indicates the resting TNF level. During the early phase, the rise of TNF level is mainly due to acute macrophage response. During the late phase, the downward trend of TNF level is mainly caused by Tregs negative feedback on TNF synthesis. (Color version of figure available online.)

SMT. Then further efforts could take place beyond that to address the effects of SMT on human immunity. In addition, it would be of interest to study whether similar mechanisms could apply to other related CAM modalities such as acupuncture and massage.

CONCLUSION

Physiological roles of TNF have recently regained attention in the biomedical research community; new findings, particularly with the discovery of the interaction between TNF and Tregs, offer new insights to understanding human immunophysiology. This progress may provide a new paradigm in understanding SMT. Based on our

literature study, we believe that TNF may mediate SMT effects by directly boosting immune surveillance and indirectly inhibiting inflammation via the sensitization and activation of Tregs, which may contribute to the clinical benefits of SMT both during wellness management and toward alleviating inflammatory pain. Thus, in addition to causing well-known neurophysiological effects, SMT may impact human immune physiology, which could offer potential novel guidance in clinical practice.

FUNDING SOURCES AND CONFLICTS OF INTEREST

No funding sources or conflicts of interest were reported for this study.

Fig 3. How could SMT use the “good molecule” features of TNF? SMT may induce an acute TNF rise, which enhances immune surveillance (in killing tumor cells, viruses, and bacteria). That acute TNF elevation may also trigger negative Tregs feedback, which inhibits inflammation. M, macrophages. Green line: stimulatory; red line: inhibitory. Other TNF-producing immune cells such as natural killer cells could also act similarly as macrophages but not drawn in the figure. Note that Tregs are omitted in the figure because they are responsible for the “bad” effects of TNF. SMT, spinal manipulation therapy; TNF, tumor necrosis factor.

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