The role of inflammation in sciatica: the contradictory effect of macrophages

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Chapter I

Introduction and general outline

"Don't count the days, make the days count"
(Muhammad Ali)

With an incidence of 1-3%, lumbar disc herniations cause a major burden for society worldwide [1]. Patients with lumbar disc herniations often suffer from disabling leg pain radiating down the dermatome, also known as sciatica. The origin of sciatica can partially be explained by mechanical compression of the nerve root by the herniated part of the disc, however, the presence of asymptomatic cases with clear nerve root compression, and vice versa symptomatic cases where clear compression is absent, illustrate that compression cannot be the only factor at play [2, 3]. In search for an additional cause for sciatica, an increasing amount of interest is being devoted to inflammation. Disc inflammation may occur if the nucleus pulposus herniates into the epidural space, where it is exposed to the systemic circulation, which creates an opportunity for macrophages to infiltrate [4]. This inflammation response is believed to irritate the nerve root, thereby exacerbating sciatica symptoms. In contrast, macrophages are also thought to play a vital role in recovery through resorption of the herniated disc material.

It follows that macrophages can be seen as a double-edged sword: on one hand, macrophage infiltration may result in an exacerbation of sciatica through expression of pro-inflammatory cytokines such as IL-6, IL8 and TNF-alpha [5-7]: the so-called 'painful inflammation response'. On the other hand, macrophages may induce a resorption process by excreting matrix metalloproteases [8], inducing apoptosis, degrading collagen fibers [9] and phagocytizing dead material [10]: the so-called 'functional inflammation response'. As of today, it remains unknown whether all patients unavoidably experience both effects or whether some mainly experience the beneficial resorption abilities while others mostly suffer from their nerve sensitizing features. Moreover, the extent of macrophage infiltration, and therefore the impact of their effects, may vary widely from patient to patient and, in many patients, macrophages are absent.

Whether macrophages will infiltrate the area with the lesioned disc and how they behave once they are there is believed to depend upon the local environment. One of these environmental factors is the type of disc herniation, which can be categorized in 2 groups: The first is called disc bulging, in which the nucleus pulposus (NP), the inner part of the disc, may bulge into the epidural space, but is maintained within the outer structure of the disc, the annulus fibrosus (AF). Therefore, the NP is not directly exposed to the epidural space. This is contrary to the extrusion, in which case the NP is extended in the epidural space due to a defect in the structural integrity of the outer layer. Because the extruded NP is more exposed to the systemic circulation in the epidural space, extrusion may result in a higher degree of neovascularization and consequently a higher degree of inflammation.

A different characteristic that could influence macrophage infiltration is the mechanism of disc extrusion: One mechanism is through an endplate avulsion (EPA), in which case the annulus fibrosus is detached from the endplate; the other is due to an annulus fibrosus tear (AFT). The important difference between these two mechanisms is the rate of vascularization between the AF and endplate. In contrast to the avascular AF and NP, the endplate is highly vascularized. In a physiological situation, the endplate supplies the NP and AF with nutrients through diffusion, which prevents inflammatory cells like macrophages from entering the NP and AF. However, when the endplate is avulsed, it is directly exposed to the ruptured blood vessels of the endplate, which may influence the rate of macrophage infiltration. This is in contrast to the AFT, in which case exposure to circulation is limited to the epidural space and no additional source of local neovascularization is present.

Another phenomenon that may be of significance for macrophage infiltration in the presence of Modic Changes (MC) in the endplate, also known as vertebral end-plate signal changes (VESC) [11]. MC are visible on the MRI and can be subdivided into 3 types: MC type 1 (MC1) is characterized by acute inflammation and bone marrow oedema, MC type 2 (MC2) by chronic inflammation and fatty marrow proliferation, and MC type 3 (MC3) by sclerosis [12, 13]. These inflammatory reactions of the endplate, visualized as MC have been proposed to be associated with slowing the recovery rate in patients that suffer from a herniated disc [14]. These characteristics of disc rupture and its local environment may not only matter for degree of macrophage infiltration, but also could be of influence on the macrophage differentiation process.

Macrophage differentiation depends on environmental factors. Each set of environmental cues will lead to distinct macrophage phenotypes, which show unique behavior and expression profiles [15]. Even though each phenotype is unique, many expression profiles can be polarized to pro- or anti-inflammatory, and their corresponding macrophage phenotypes are often referred to as M1 (pro-inflammatory) or M2 (anti-inflammatory) macrophages [16]. The expression profile of M1 macrophage has been associated with exacerbation of pain symptoms [6], whereas the expression profile of M2 is involved in inflammation modulation, tissue repair and remodelling [5, 15, 17, 18]. Hence, polarization of macrophages may have a tremendous impact on the sciatic symptoms: through their impact on nerve irritation and sensitization, and through their impact on the resorption of the herniated disc. As of today, only limited evidence is available on what influences the extent of macrophage infiltration [15], and even less on what influences macrophage differentiation in the herniated disc. A better understanding of how the inflammation profile in response to the disc lesion affects sciatica symptoms and the rate of recovery could lead to new, more personalized treatment strategies.

Aims and outline of this study:

1. It is crucial to have an overview of what is currently known on the effects of macrophage infiltration and their pro/anti-inflammatory expression profile on sciatic symptoms. Therefore, the first aim of this study is to systematically review all known associations between (M1/M2) macrophage infiltration or their related inflammation factors, and clinical outcomes in patients suffering from a lumbar disc herniation (Chapter 2).

2. The beneficial effect of macrophage infiltration is supposedly through inducing a resorption process, which has never been verified in a clinical trial. Moreover, previous studies have only focused on the effects of macrophage infiltration in general and have failed to assess the interactions with the local environment. The second aim of this study is to associate macrophage infiltration with disc resorption on MRI (Chapter 3) and with clinical recovery during follow-up after surgery (Chapter 4). More interestingly, since an interaction effect with the environment is to be expected, these associations will be assessed for patients with and without MC separately, and the influence of bulging versus extruded discs on the effect of macrophage infiltration will also be considered.

3. In order to integrate macrophage infiltration and inflammation in the clinical decision process a non-invasive biomarker would be required. Gadolinium enhancement in MRI is explored to have potential as such a biomarker. Hence the third aim of this study is to evaluate gadolinium enhancement as tool to assess macrophage infiltration of the disc (Chapter 5).

4. Although some studies have reported on altered gene expression profiles of MC, the effect of EPA on the inflammation profile remains to be elucidated. Hence the fourth aim of this study is to elucidate the effect of endplate pathology on the inflammatory profile of the lesioned disc material, using a proteomic and bioinformatic approach (Chapter 6).

5. Since altered behavior of macrophages is believed to be caused by altered differentiation, the fifth aim of this study is to identify the type of macrophage (M1 vs M2) found in disc herniations, and whether it is influenced by the presence of MC (Chapter 7).

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