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EDITORIAL

NERVE-MAST CELL-NERVE GROWTH FACTOR LINK: THE MAST CELL AS YIN-YANG MODULATOR IN INFLAMMATION AND FIBROSIS

"Perhaps the situation at present is similar to that of the Holy elephant which had a hundred names, the real one being the hundred and first, known only to the elephant himself."

Albert Szent-Gyorgyi
Retrospect and Apology. In: Milhorat AT, editor. Exploratory concepts in muscular dystrophy and related disorders. New York, Excerpta Medica Foundation, 1966; 112-114

• Inflammation and fibroproliferation are biological responses aiming at recovering from injury. Wound healing is considered a paradigm of such a homeostatic phenomenon. However, what begins as a protective response, in excess becomes a damaging process we call chronic inflammatory-fibroproliferative disease.

Celsus's description (1st century AD) of inflammation signs includes *rubor et tumor cum calor et dolor.* For many years the inflammatory process has been thought of purely in terms of interactions involving leukocyte infiltration and fibroblast activation. Increasingly, however, neural cells have been shown to play a particularly important role in it, including interactions between nerves and mast cells (MC) (1-3). The article by Aloe *et al* (4) in this volume of *Biomedical Reviews* sheds considerable light on the potential significance of MC and nerve growth factor (NGF) in autoimmune-inflammatory diseases.

Historically, the discovery of MC is usually attributed to Paul Ehrlich in 1878, although these cells were first recognized by von Recklinghausen in 1863. Ehrlich observed that MC were commonly located in connective tissue near blood vessels and *nenes,* as well as in *inflammatory and tumor lesions.* At present there is evidence that (i) MC can be classified into connective tissue and mucosal subsets, and (ii) MC synthesize and, when activated, release biologically active molecules, e.g. eicosanoids, cytokines and growth factors, including the neurotrophic factors NGF (5) and leukemia inhibitory factor (LIF) (2,3). Last but not least, connective tissue MC are the richest cellular source of heparin proteoglycan, histamine, tryptase and chymase (6), and preformed, secretion granule-stored tumor necrosis factor-a (TNF-a), a highly potent inflammatory and fibrogenic cytokine (1).

The recent great advance relevant to MC studies occurred in 1977 when Aloe and Levi-Montalcini established the NGF-induced MC proliferation in different tissues of NGF-injected rats (7). This insight into the biology of NGF gives a special meaning to the nerve-MC bidirectional link, involving an immunotrophic action of the classical neurotrophin NGF (Fig.l). Further, MC-fibroblast interactions (8) and mast cell growth factor (MGF; synonyms: stem cell factor, c-kit ligand; see Bankl *et al* [9] in this volume *of Biomedical Reviews)* were recognized to play a pivotal role in the biology of MC. Even more intriguing is the possibility that the immunotrophin MGF exerts a neurotrophic action (10). Thus the nerve-MC bidirectional link was further extended (Fig.2). These new concepts about MC, i.e. paracrine/autocrine interactions between nerves and MC (1-3), MC and fibroblasts (8), and nerves, MC and effector cells (11), are now considered not only in allergic, parasitic and neoplastic reactions, but also in a number of disease processes featured by inflammation and fibrosis (Table 1, Refs shown in parentheses).

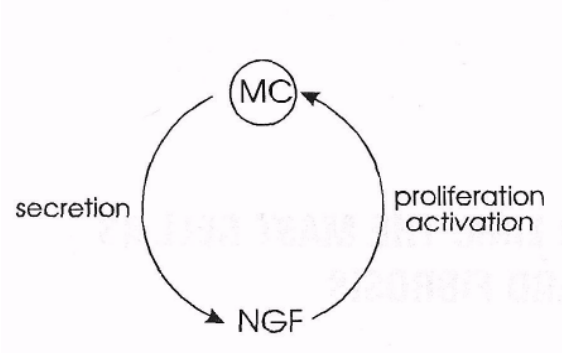

Figure 1. *Mast cells (MC) are source of and target for nerve growth factor (NGF).*

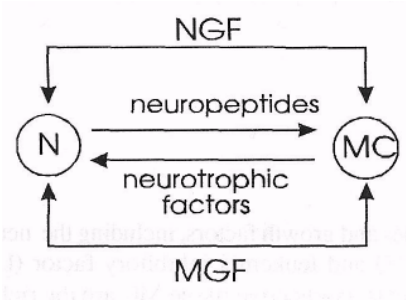

Figure *2. The nerve (N)-mast cell (MC) bidirectional link also involves both neurotrophic and immunotrophic actions of nerve growth factor (NGF) and mast cell growth factor (MGF).*

Possible ways of interactions between nerves, MC and cytokines, including neurotrophic factors, in the development of inflammation and fibrosis are schematically presented in Fig.3,4 (Refs shown in parentheses). We, as Aloe *et al* (4), suppose that a discordant equilibrium, in which MC-derived inflammatory and fibrogenic stimulators exceed inhibitors, participates in progression of inflammation and fibrosis. Thus, MC via synthesis and release of such molecules may be considered a modulator operating in a *yin-yang* manner in the regression, delay, or progression of these disease processes (Table 2, Refs shown in parentheses). Of course, other immune cells, e.g. macrophages and lymphocytes, as well as their interactions with the neuroendocrine system (3 9), may also be particularly important in this aspect. In the context of this Editorial, it is worth mentioning that the immunotrophic action of NGF involves these immune cells too (4, their Refs 37-47).

A lot of issues can be raised in relation to the possible participation of nerve-MC-NGF-MGF link in the pathogenesis of inflammatory-fibroproliferative diseases listed in Table 1. For example, Aloe *et al* (4) present data of correlative increase in MC number and NGF level in autoimmune diseases, but a possible involvement of MGF remains unreported yet. Similarly, MGF action on cardiac MC was studied by Bankl *et al* (9) and Sperr *et al* (40). However, a possible importance of NGF in the biology of these cells was not appreciated, although a separate report clearly showed a significantly high NGF level in heart atrium (41), i.e. where a considerable amount of MC was found (9,40). In addition, recent reports show that NGF and other neurotrophins (42), including LIF (35), play an important role in regulating the response of vascular smooth muscle cells to injury. Again, inMC-rich atherosclerotic lesions (22,23), neither NGF nor MGF were examined. Hopefully, an integrative research approach (cf Table 1) focusing on cardiovascular nerve-MC-NGF-MGF link may bring new insights into car-

Table 1. *Mast cell-associated diseases featured by inflammatory-fibroproliferative responses*

Diseases		
Mast cell/NGF-associated	***Mast cell/nerve-associated***	***Mast cell-associated***
rheumatoid arthritis (4,12)	rheumatoid arthritis (13)	scleroderma (6)
multiple sclerosis (4,12)	gout (13)	pulmonary fibrosis (14,20)
systemic sclerosis (4,12)	bronchial asthma (2,14)	liver cirrhosis (21)
systemic lupus erythematosus (4,12)	chronic rhinitis (15)	atherosclerosis (22,23)
	Crohn's disease (2,13)	chronic graft-versus-host diseases (24)
	chronic ulcerative colitis (2,13)	keloid (19)
	oral mucosa inflammation (16)	Behçet's disease (19)
	temporal arteritis (17,18)	idiopathic male infertility (25)
	cluster headache (17,18)	interstitial cystitis (26)
	psoriasis (6,19)	Duchenne muscular dystrophy (27)
	lichen planus (6,19)	

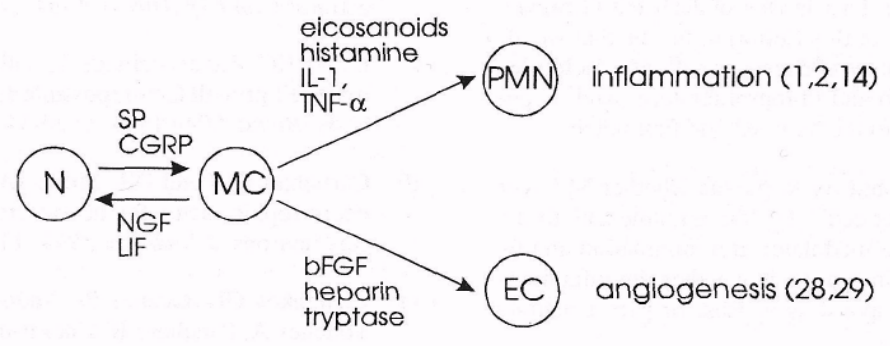

Figure 3. Cell-mediator interactions leading to inflammation and angiogenesis. N - neural cell, MC - mast cell, PMN - polymorphonuclear leukocyte, EC - endothelial cell, SP - substance P, and CGRP - calcitonin gene-related peptide (these are shown as examples of well-known proinflammatory neuropeptides), IL-1 - interleukin-1, bFGF - basic fibroblast growth factor. For the rest abbreviations, see the text.

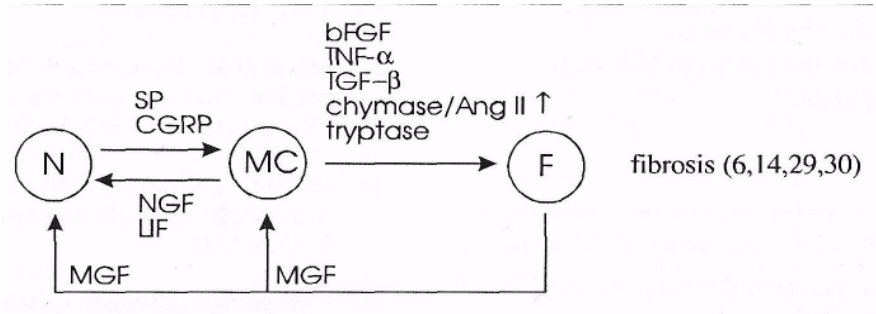

Figure 4. Cell-mediator interactions leading to proliferation and fibrosis. N - neural cell, MC - mast cell, F - fibroblast, TGF-f} - transforming growth factor-^, Ang 11 - angiotensin II. Note: (i) substance P exerts mitogenic effect both on fibroblasts and smooth muscle cells (31,32), and (ii) MC may also produce collagen (33).

Table 2. Mast cell-derived molecules as yin-yang modulators in inflammation and fibrosis

Yin (inhibitory counterpart)	*Yang* (stimulatory counterpart)
heparin* (34)	eicosanoids (1,14)
chymase*/SP↓ (6,14)	chymase/procollagenase ↑ (37)
NGF (4,12)	chymase/Ang II ↑ (6,14)
LIF (35)	tryptase (30)
IL-4 (4)	histamine (38)
VIP (36)	TNF-α (1,2,6)
NO (11)	IL-1 (1,2,6)
	bFGF (29)
	TGF-β (1,2)

*Note: this molecule may have both *yin* and *yang* potential.
VIP - vasoactive intestinal polypeptide, NO - nitric oxide.

diovascular diseases of inflammatory-fibroproliferative nature (11,43). Perhaps, "we are already beginning to witness the change" (39) in our understanding of inflammation and fibrosis, as well as other nerve-MC-NGF-associated phenomena. A few years ago, it would seem premature to think that the submandibular gland, the richest source of NGF and a densely innervated effector tissue that also contains significant amount of MC, may produce molecules involved in regulation of inflammatory (44, also see Mathison [45] in this volume *of Biomedical Reviews)* and behavioral (46,47) responses. In effect, optimization of mechanisms for maintaining and/or restoring nerve-MC-NGF-MGFhomeostatic functions following tissue inflammatory stimuli may lead to the development of new, MC-directed therapies for inflammatory-fibroproliferative diseases. Examples include angiotensin-converting enzyme inhibitors (21), MC stabilizing drugs (24,38), opioid receptor antagonists (36), anti-TNF-a drugs (48-51), adenosine A_3-receptor antagonists (52), histamine H_3-receptor agonists (53), and tryptase inhibitors (54).

Of course, the questions to be addressed remain rather more than the answers provided. This, in view of the Szent-Gyorgyi's thought at the beginning of this Editorial, means that we already are aware of the names of dozens of cells and molecules that govern inflammation and fibroproliferation. And, hopefully, we are forwarding to the hundred and first name.

In further studies we would try to pursue whether MC will prove to stand for "master cell" (1), "the immune gate to the brain" (55), and *yin-yang* modulator in inflammation and fibrosis. And, even more intriguing is whether the inflammatory-fibroproliferative response is at least in part a neural-mastokine phenomenon.

George N. Chaldakov', Peter I. Ghenev[2], Kamen Valchanov[1,2], Anton Tonchev[1,2], andRuzha Pancheva[1,2]

laboratory of Electron Microscopy,
Department of Anatomy and Histology,
^Department of General and Clinical Pathology,
Medical University of Varna
BG-9002 Varna
Bulgaria

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