The legacy of a maestro

S. Bombardieri, C. Baldini

Stefano Bombardieri, MD, Professor of Rheumatology and Head, Rheumatology Unit, and Chiara Baldini, MD, Rheumatology Unit, Department of Internal Medicine, University of Pisa, Pisa, Italy.

In May 2002, during his last trip to Italy Carwile LeRoy tragically passed away. This supplement was conceived to provide an overview of present knowledge and new prospectives in all of Carwile LeRoy's principal fields of interest. For each area his vital contribution is acknowledged and the results of the most recent research are presented. In our view this is the best way to pay homage to him and his work, especially – but not only – his extraordinary contributions to the field of scleroderma.

In addition to his discoveries regarding the etio-pathogenesis of SSc, in 1980 LeRoy proposed for the first time the term "Undifferentiated Connective Tissue Syndromes" (UCTD) to identify patients with a permanent but undefined clinical and serological profile in comparison to those who eventually develop defined connective tissue diseases or mixed/overlapping syndromes (1). LeRoy can be therefore considered the father not only of SSc but also of UCTD. For this reason a review of UCTD as a distinct clinical entity has been included; it examines the recent literature and discusses the prospects for improving the sensitivity and specificity of the existing preliminary classification criteria (2).

Systemic scleroderma (SSc) is one of the most obscure and fascinating multisystem diseases known. While the aetiology of the disease remains a mystery and its pathogenesis is for the most part unclear, LeRoy's work laid the basis for our understanding of the intriguing interactions between immunological abnormalities, vasculopathy and fibroblast aberrations which play a crucial role in cutaneous and visceral sclerosis (3). With this supplement, today's leaders in systemic sclerosis research – all of whom were LeRoy's pupils – have sought to provide an update on the latest developments in SSc and to express their gratitude to their teacher and friend.

The main body of the supplement is dedicated to SSc. The overview begins with the proposal of a working classification system for SSc (4) based on a thorough analysis of what is presently known about the pathogenesis of SSc from vascular involvement and endothelial injury to the paradigm of microchimerism and the principal alterations in scleroderma fibroblasts. To shed light on the main pathogenetic aspects of fibrosis, the tight skin mouse is proposed as an animal model of SSc (5, 6). An overview of the treatment of early diffuse cutaneous SSc patients with low-dose corticosteroids from a dermatologic perspective is offered (7).

The vascular hypothesis of the pathogenesis of SSc and the observation that scleroderma fibroblasts synthesise more collagen *in vitro* than fibroblasts from healthy subjects represent perhaps LeRoy's most important contributions to the field of microcirculatory hypertension. Therefore, the excursus on the pathogenesis of SSc begins with an article by Kahaleh which summarizes our current understanding of vascular involvement in SSc and illustrates some of the most recent studies on endothelial cell (EC) apoptosis as an early event in the pathogenesis of SSc (8, 9).

Among the possible mechanism of EC apoptosis induction, particular attention has focused on cytomegalovirus (CMV), based on LeRoy's original hypothesis regarding the possible role of this virus as a trigger of SSc (10). Therefore two papers, by Pandey and Markiewicz respectively, explore the complex and fascinating relationship between CMV and SSc from different perspectives. Pandey discusses whether the immunoglobulin genes GM and KM which are involved in the production of anticentromere and anti-fibrillin I antibodies may not also influence the generation of IgG antibodies to CMV in patients with SSc (11). Markiewicz and colleagues examine the role of the immediate early protein (IE-1) of CMV in the induction of connective tissue growth factor (CTGF) in human dermal fibroblasts; the authors hypothesise that a transient or limited reactivation of CMV may intervene in matrix remodelling in SSc (12).

E. Carwile LeRoy, *MD*
(1933 – 2002)

In the vascular hypothesis of SSc, one of the most significant events is vascular dysfunction characterised by an alteration in vascular permeability and, most crucially, by a dysregulation in the vascular tone with an imbalance between the production of endothelin and nitric oxide. EC play a central role in this process, as the research by Milner *et al.* underlines. Their study in fact

shows for the first time that dermal microvascular endothelial cells express substance P mRNA and that under particular conditions the endothelial release of both substance P and endothelin is enhanced. An open question remains as to exactly how an alteration in vascular tone may arise from the interactions between these substances (13).

Whatever the mechanism, one consequence of vascular injury is the release of circulating vascular markers – not only endothelin I and nitric oxide, but also soluble adhesion molecules, prostacyclin, von Willebrand factors and coagulation and fibrinolysis products, including activated thrombin (14). Regarding the cellular effects of thrombin, the paper by Ludwicka *et al.* analyses the role played by it in the process of fibrosis, particularly in fibrosis of the lung. Pulmonary fibrosis is one of the most frequent causes of death in SSc, either directly or as a consequence of secondary pulmonary hypertension (15). Thrombin is involved in all the steps of fibrosis from the differentiation of fibroblasts into myofibroblasts to the activation of EC and the secretion of several profibrotic and angiogenic factors. Since thrombin acts via a protease-activated receptor (PAR–1), the authors suggest how this could lead to a new therapeutic strategy for the management of scleroderma lung fibrosis (16).

In addition to vascular dysfunction, many other mechanism are involved in the pathogenesis of SSc, beginning with microchimerism and fibroblast aberration. In recent years important progress has been made in both of these areas. Increased attention has been devoted to a particular subset of T lymphocytes exhibiting the γ/δ receptor, which is likely to suppress the maternal anti-fetal immune response via TGFβ production, as is summarised in the paper by Giacomelli *et al*. (17).

The second part of the supplement is dedicated to studies on scleroderma fibroblasts. Trojanowska presents a review of the transcription factors that are deregulated in the SSc fibroblast (18). The papers by Korn and by Gardner *et al.* describe fibroblast gene regulation *in vitro* by TGF-β and suggest that an increase sensitivity or responsiveness to TGF-β might be involved in the fibrosis process (19, 20). Luchetti *et al*. report that the main feature of the activated SSc fibroblast is the expression of pentraxin (PTX3), which is involved in the innate resistance to pathogens, in inflammatory reactions and in the clearance of self-components. The authors propose that PTX3 over-expression could be interpreted as an effort to prevent autoimmune reactions to autoantigens released by oxidative stress (21). Eckes & Krieg describe the adaptive phenotype of fibroblasts residing in the dermal connective tissue in response to tensile forces and propose that mechanical tension can be considered an additional important regulatory parameter (22).

We hope that the supplement will give an idea of the scientific legacy that Carwile LeRoy has left to rheumatology and to those who suffer from this complex disease, a legacy of immense importance for – as is well known – when a true maestro leaves, his orchestra continues to play.

References

1. MOSCA M, BALDINI C, BOMBARDIERI S: Undifferentiated connective tissue diseases in 2004. *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S14-S18.
2. LEROY EC, MARICQ HR, KAHALEH MB: Undifferentiated connective tissue syndromes. *Arthritis Rheum* 1980; 23: 341-3.
3. CAMPBELL PM, LEROY EC: Pathogenesis of systemic sclerosis: a vascular hypothesis. *Semin Arthritis Rheum* 1975; 4: 351-68
4. RAND MARICQ H, VALTER I: A working classification of scleroderma spectrum disorders: A proposal and the results of testing on a sample of patients. *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S5-S13.
5. CARREIRA PE, DAHM MW, NORRIS JS: Transcription activity in fibroblasts from the adult tight skin (TSK) mouse. *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S77-S80.
6. PABLOS JL, EVERETT ET, NORRIS JS: The tight skin mouse: an animal model of systemic sclerosis. *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S81-S85.
7. TAKEHARA K: Treatment of early diffuse cutaneous systemic sclerosis patients in Japan with low dose corticosteroids for skin involvement. *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S87-S89.
8. KAHALEH MB: Vacular involvement in systemic sclerosis (SSc). *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S19-S23.
9. SGNONC R, GRUSCHWITZ MS, DIETRICH H, RECHEIS H, GERSHWIN ME, WICK G: Endothelial cell apoptosis in a primary pathogenetic event underlying skin lesions in avian and human scleroderma. *J Clin Invest* 1996; 98: 785-92.
10. PANDEY JP, LEROY EC: Human cytomegalovirus and the vasculopathies of autoimmune diseases (especially scleroderma), allograft rejection, and coronary restenosis. *Arthritis Rheum* 1998; 41: 10-5.
11. PANDLEY JP: Immunoglobulin GM genes and IgG antibodies to cytomegalovirus in patients with systemic sclerosis. *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S35-S37.
12. MARKIEWICZ M, SMITH EA, RUBINCHIK S, DONG JY, TROJANOWSKA M, LEROY EC: The 72-kilodalton IE-1 protein of human cytomegalovirus (HCMV) is a potent inducer of connective tissue growth factor (CTGF) in human dermal fibroblasts. *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S31-S34.
13. MILNER P, BODIN P, GUIDUCCI S *et al.*: Regulation of substance P mRNA expression in human dermal microvascular endothelial cells. *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S24-S27.
14. KAHALEH B, MEYER O, SCORZA R: Assessment of vascular involvement. *Clin Exp Rheumatol* 2003; 21(Suppl 29): S9-14.
15. MATUCCI-CERINIC M, D'ANGELO S, DENTON CP, VLACHOYIANNOPOULOS P, SILVER R: Assessment of lung involvement. *Clin Exp Rheumatol* 2003; 21 (Suppl 29): S19-S23.
16. LUDWICKA-BRADLEY A, BOGATKEVICH G, SILVER RM: Thrombin-mediated cellular events in pulmonary fibrosis associated with systemic sclerosis (scleroderma). *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S38-S46.
17. GIACOMELLI R, CIPRIANI P, FULMINIS A, NELSON JS, MATUCCI CERINIC M: γ/δ T cells in placenta and skin: their different functions may support the paradigm of microchimerism in systemic sclerosis. *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S28-S30.
18. TROJANOSKA M: What did we learn by studying fibroblasts? *Clin Exp Rheumatol* 2004; 22: (4 Suppl 33): S59-S63.
19. KORN JH: What's wrong with the scleroderma fibroblast? *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S64-S65.
20. GARDNER H, STREHLOW D, BRADLEY L *et al.*: Global expression analysis of the fibroblast transcriptional response to TGFβ. *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S47-S57.
21. LUCHETTI MM, SAMBO P, MAJLINGOVA P *et al.*: Scleroderma fibroblasts constitutively express the long pentraxin PTX3. *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S66-S72.
22. ECKES B, KRIEG T: Regulation of connective tissue homeostasis in the skin by mechanical forces. *Clin Exp Rheumatol* 2004; 22: (Suppl 33): S73-S76.