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Feature Articles

Phenotypic Features of Stromal Cells in Normal, Premalignant and Malignant Conditions

Annette Schmitt-Gräff and Giulio Gabbiani

INTRODUCTION

THE DYNAMIC cooperation between organotypic cell populations and their mesenchymal stroma is a common theme in embryonic development, tissue repair throughout life, and malignancy. Evidence is accumulating that extracellular matrix components, soluble cellular products and direct cell-to-cell contacts constitute microenvironmental signals implicated in tissue morphogenesis as well as in carcinogenesis [1–6]. Local perturbations in the tumour–host interactions are considered to play a key role in cancer development, angiogenesis, invasion and metastasis [7–12]. Moreover, it is well recognised that the bone marrow stroma is of crucial importance for the coordinated developmental pathway of the haematopoietic stem cells and their progeny [13], while leukaemic populations escape such positive and negative regulatory influences [14, 15]. The purpose of this review is to briefly highlight the phenotypic features of stromal fibroblasts in different types of premalignant and malignant situations. Previous well-referred reviews have covered the area of stromal regulation of epithelial functions [9, 16, 17].

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HETEROGENEITY OF FIBROBLASTIC CELLS IN NORMAL AND PATHOLOGICAL TISSUES

The information gathered from numerous *in vivo* and *in vitro* studies supports the view that fibroblastic cells present in normal

and especially pathological tissues display a phenotypic and functional heterogeneity [18]. This is reflected by morphological traits, cytoskeletal features and secretion of extracellular matrix components, proteolytic enzymes and growth factors [19–22]. Our laboratory has been interested in the diversity of phenotypic features of fibroblastic populations. Connective tissue fibroblasts contain a well-developed rough endoplasmic reticulum, small amounts of microfilaments and are generally decorated by antibodies against vimentin, and not by antibodies against smooth muscle markers such as α-smooth muscle (SM) actin, desmin or SM myosin [23, 24]. Pathological settings associated with tissue remodelling and fibrogenesis are characterised by the appearance of stromal cells with ultrastructural features intermediate between those of typical fibroblasts and those of smooth muscle cells (SMC). This cell type was first observed in granulation tissue and named myofibroblast (MF) [24–26]. At the ultrastructural level, MFs are characterised by abundant bundles of microfilaments arranged parallel to the long axis of the cell [26]. MFs may express temporary or permanent cytoskeletal proteins indicating a SM differentiation. Various permutations of the co-expression of vimentin, α-SM actin and desmin have been observed [27]. Immunoelectron microscopic observations have documented that α-SM actin is located within microfilament bundles of MFs present in granulation tissue and liver fibrosis [28, 29]. In experimental, full thickness wound granulation tissue, MFs express α-SM actin only temporarily during the period of active retraction, indicating a phenotypic plasticity of stromal cells which is probably related to the modulation of cellular functions [28]. The presence of stress fibres and a well-developed rough endoplasmic reticulum are suggestive of both contractile and synthetic activities of MFs [24]. Moreover, in fibrocontractive diseases and desmoplasia, MFs with SM features are seen permanently, further confirming their role in the production of retractile phenomena [27].

MYOFIBROBLASTS IN THE STROMA OF NEOPLASTIC LESIONS

It is generally recognised that fibroblasts may proliferate and elaborate excessive amounts of extracellular matrix, especially type III and V collagens, in the vicinity of invasive neoplasias [30, 31]. These productive changes are often associated with the presence of bloodborne inflammatory cells, such as macrophages, lymphocytes and mast cells [32]. The hallmark of this fibrotic process is the phenotypic modulation of stromal cells into MFs [26, 33]. Numerous observations based on a large series of surgical specimens indicate that MFs expressing α-SM actin are widely represented in the stromal desmoplasia of epithelial tumours [18, 24, 34, 35]. Desmin is only present in a limited proportion of such MFs [27] and SM myosin is exceptional, further supporting the fibroblastic nature of these cells. The appearance of α-SM actin is allegedly associated with the generation of contractile forces by the stroma responsible for retraction phenomena of organ capsules, serosal tissue or the skin covering neoplastic lesions. However, it is difficult to envisage that MFs of the stroma reaction to epithelial tumours exert only retractile activities, therefore it appears likely that the development of SM features coincides with, or is related to, other more subtle biochemical activities of these cells, which remain to be defined. Stroma reaction is well known in conditions such as invasive ductal mammary carcinomas, umbilicated metastatic tumours in the liver and 'scar carcinomas' of the lung, which are now rather considered as primary neoplasias provoking an important desmoplasia [26, 29, 36]. In nodular-sclerosing Hodgkin's disease, α-SM actin-expressing MFs are encountered along developing fibrotic bands and are less frequent in dense birefrigent connective tissue ([37] and A.S.-G., personal observation). Scattered α-SM actin-positive MFs may be seen in some types of non-Hodgkin lymphomas, such as follicular centre cell lymphomas with sclerosis or peripheral T-cell lymphomas with a more delicate compartmentalisation (A.S.-G., personal observation). Staining for α-SM actin may reveal positive MFs intermingled with negative tumour cells in soft tissue sarcomas, such as malignant fibrous histiocytomas or liposarcomas, while it brightly decorates benign, or inconsistently malignant SM tumours ([26] and A.S.-G., personal observation). Interestingly, in tumours originating from cells rich in α-SM actin such as leiomyosarcoma, the expression of this protein is limited only to well-differentiated variants [38]. In tumours of the ovary, α-SM actin labelling is not restricted to desmoplastic stromal reactions but also includes stroma which is an inherent part of biphasic neoplasms such as mesodermal (müllerian) mixed tumours [39].

It is worth noting that the presence of α-SM actin-positive, but desmin-negative cells is not restricted to desmoplasia with dense masses of fibrous stroma, but may be encountered in the surroundings of tumour cells lacking overt productive changes such as small foci of metastatic cells in liver or bone marrow [40, 41]. This observation is in accordance with the concept that the expression of α-SM actin by mesenchymal cells may appear earlier than the deposition of increased amounts of extracellular matrix observed in experimental models of fibrogenesis [29].

Cytoskeletal analysis has revealed that α-SM actin expressing mesenchymal cells may be a feature of premalignant lesions or intraepithelial neoplasia. Villous adenomas of the colon, which may develop into cancer, contain α-SM actin-positive cells in the lamina propria of papillary fronds projecting perpendicularly from the muscularis mucosae [42]. It is now well known that benign breast disease encompasses a wide range of patterns with an increased risk of subsequent carcinoma development, essentially confined to those with florid or atypical hyperplasia. Fibroblast staining for α-SM actin has been observed in the breast mesenchyme surrounding foci of intraductal epithelial hyperplasia, papillomatosis and sclerosing adenosis [35]. An immunohistochemical study of epithelial malignancy in the uterine cervix has revealed that α-SM actin-positive mesenchymal cells accumulate during cervical intraepithelial neoplasia [43]. A semi-quantitative evaluation suggested a correlation between the degree of stromal staining and the grading of the lesion [43]. This feature may be of potential relevance when considering the criteria for cervical diagnosis. Thus, SM differentiation features of stromal cells is not pathognomonic for invasive cancer, but may be present even in the connective tissue adjacent to epithelial proliferations or intraepithelial neoplasias, which, at least in part, may result in the development of invasive malignant growth (Fig. 1a, b). This suggests that epithelial–stromal signalling may be transduced even when the basement membrane integrity is maintained.

While MFs in healing wounds and desmoplasia around primary and metastatic malignant growth in large variety of organs are considered to derive from local fibroblasts, in some tissues, such as liver or bone marrow, specialised mesenchymal cells including hepatic perisinusoidal or fat-storing (Ito) cells and subpopulations of bone marrow stroma are probably involved in fibrotic reaction to malignant growth [40, 41]. *In vivo* and *in vitro* observations have indicated that the expression of α-SM actin by bone marrow stromal cells is inversely related to

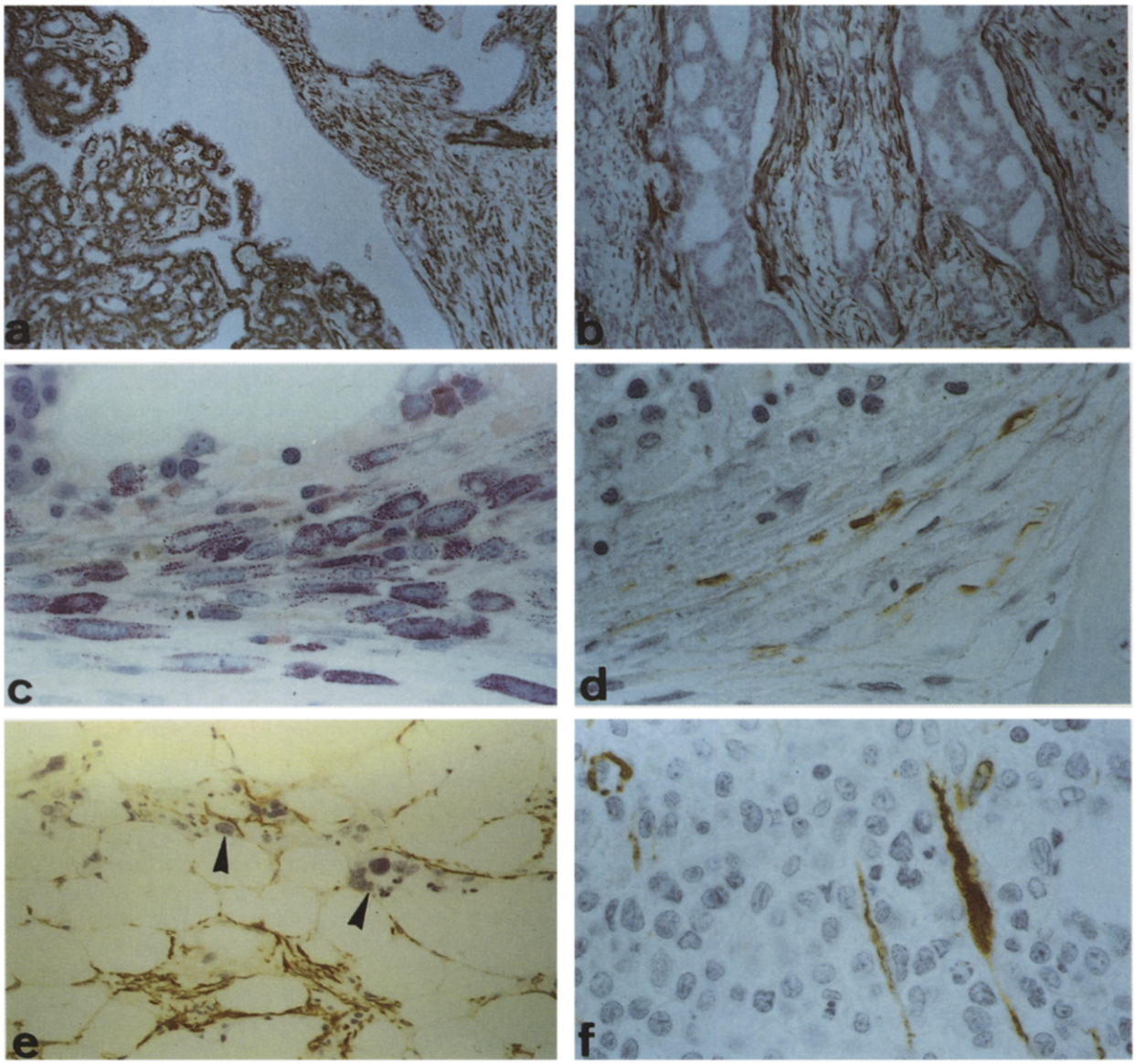

Fig. 1. Immunohistochemical detection of α-SM actin in non-malignant and malignant situations. (a) α-SM actin is localised in the myoepithelium covering the fibrovascular core of the arborescent front of a benign intraductal papilloma and in stromal cells of the periductal breast mesenchyme (× 250) as well as (b) in the desmoplastic stromal reaction to infiltrating ductal breast carcinoma (× 400). (c) Bone marrow specimen from a patient with systemic mastocytosis showing peritrabecular zones of fibrosis containing abundant mast cells (Giemsa stain × 1000) accompanied by (d) the appearance of α-SM actin-positive stromal cells (× 1000). (e) Characteristic pattern of α-SM actin expressing bone marrow stromal cells within zones of patchy collagenisation in agnogenic myeloid metaplasia (× 250; arrowheads: cluster of atypical megakaryocytes) and (f) within the slightly increased reticulin fibre network of acute myelomonocytic (M4) leukaemia (× 1000).

haematopoietic activity [40, 44]. This phenotype is present in bone marrow remodelling during fetal life and may reappear in different settings associated with a reduced or neoplastic haematopoiesis [44]. Monoclonal haematopoiesis present in chronic myeloproliferative disorders, especially agnogenic myeloid metaplasia, has a tendency to generate myelofibrosis via stimulation of stromal cells by growth factors released from megakaryocytes. This process seems to be reflected by the appearance of α-SM actin-positive MFs in close spatial relationship with neoplastic megakaryocytes [40]. This cell type is also a characteristic constituent of the fibrotic bone marrow stroma in other conditions such as hairy-cell leukaemia, systemic mastocytosis, or cancer metastases [40] (Fig. 1c–f). Follow-up studies in hairy-cell leukaemia indicate that this actin isoform may disappear from stromal cells when treatment results in a regression of leukaemic infiltration and reticulin fibrosis (A.S.-G., personal observation). Thus, the SM-like phenotype of stromal cells appears to be, at least in part, a reversible feature with possible similarities to normal repair phenomena.

CONCLUSION

From the currently available information, it appears that stroma may be an active participant in the development and progression of cancer [8, 16, 17]. Tissue transplantation experiments indicate that in some models, stromal cells may be involved in the process of viral or chemical carcinogenesis [2, 45, 46]. According to Dexter *et al.* [47], certain oncogenes resulting in leukaemia affect primarily stromal cells. Recently, a new growth factor, the c-*kit*-ligand, produced by bone marrow stroma and its receptor on haematopoietic cells has been ident-

ified [48]. A role of this receptor–ligand pair for the growth regulation of leukaemias remains to be elucidated [15]. Work from several laboratories, including ours, have shown that fibroblastic stromal cells may express in normal and pathological settings phenotypic features which have been previously considered typical of SM cells [18, 19]. This feature is regulated differently in fibroblastic cells when compared to SMC suggesting that it may be related to functions other than contraction [19]; however, these functions remain presently largely unknown. Further work along these lines may be useful for the understanding of stromal–epithelial interactions during carcinogenesis. In any event the expression of α-SM actin in stromal cells appears to be, in certain situations, a marker of epithelial precancerous changes.

During the last 10 years, the processes inducing extracellular proteolysis have been intensively explored. The imbalance of matrix degradation favouring tumour invasion has shown to be due not only to the secretion of proteolytic enzymes by the malignant cells, but also by the stroma. Thus, stromal cells surrounding invasive breast carcinomas express the metalloproteinase gene stromelysine-3 and may contribute not only to the lytic process, but perhaps also to the desmoplastic reaction [49].

Desmoplasia is generally considered as a response of host cells to inductive stimuli exerted by tumours cells [50]. Stimulation of stromal fibroblasts may be mediated through various pathways of signalling such as cytokines or extracellular matrix. Cytokines with a well-established influence on mesenchymal cell proliferation and differentiation including TGF-β, PDGF and GM-CSF have also been proposed as putative factors modulating the differentiation repertoire of stromal cells. However, after local *in vivo* application, only GM-CFS has been shown up to now to stimulate α-SM actin synthesis in MFs [51]. Further studies are needed to clarify the effects of different cytokines, which may modulate the cytoskeletal protein expression of fibroblastic cells. Of special interest is the observation that SM differentiation features of stromal cells are not restricted to invasive malignant growth but may even be present in the surroundings of intraepithelial neoplasia and epithelial proliferation with a predisposition to malignant transformation [35, 42, 43]. The appearance of an α-SM actin-positive stromal phenotype may reflect changes of the microenvironment present already in early stages of tumorigenesis. Studies of the phenotypic modulations of stromal cells may help to understand the complex interplay between neoplastic tissue and its surroundings.

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The Management of Hodgkin's Disease in Relapse after Primary Radiation Therapy

Richard T. Hoppe

Approximately 20–25% of patients with stage I–II Hodgkin's disease treated initially with irradiation alone will experience a relapse of disease. Restaging at the time of relapse provides a useful prognostic indicator and may help in the selection of salvage therapy. Systemic treatment is indicated in nearly all patients. In the Stanford experience, 109 patients who relapsed were treated with MOPP (or MOPP-like chemotherapy) with or without local irradiation. The actuarial 10-year survival and freedom from second relapse were both 57%. Important prognostic factors included 'relapse stage' (IA vs. II–IIIA vs. I–IIIB or IV) and type of salvage therapy (combined modality vs. chemotherapy alone). Important issues in management of these patients include the selection of chemotherapy agents, whether to incorporate localised irradiation, and the use of even more aggressive salvage treatment programs, such as autologous bone marrow transplantation, in selected patients with a very poor prognosis.
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INTRODUCTION

APPROXIMATELY 75–80% of patients with early stage Hodgkin's disease selected for treatment with irradiation alone, can expect to achieve long-term disease-free survival after treatment with that modality. The management of the 20–25% of patients who relapse poses a significant clinical challenge. Important issues to address include documentation of the initial relapse, an evaluation of the extent of disease at the time of relapses, and selection of the salvage treatment program. This manuscript will deal with each of these issues.

Approximately 75% of relapses after initial treatment with irradiation alone will occur within the first 3-year follow-up