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Review

Emerging role of tissue lectins as microenvironmental effectors in tumors and wounds

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Summary. Detailed comparative analysis of at first sight not related process cascades is a means toward this aim: to trace common effector mechanisms and hereby eventually inspire innovative routes for therapeutic management. Following this concept, promotion of tumor progression by stroma, especially cancer-associated fibroblasts and smooth muscle actin-positive myofibroblasts, and beneficial activity of respective cells in wound healing have helped to delineate the involvement of endogenous lectins of the family of galectins. In addition to initiating conversion of fibroblasts to myofibroblasts, galectin-1 instructs the cells to produce a structurally complex extracellular matrix. This bioscaffold is useful for keratinocyte culture, also apparently operative in ameliorating wound healing. These functional aspects encourage to study in detail how lectin-(glycan) counterreceptor display is orchestrated. Such insights are assumed to have potential to contribute to rationally manipulate stem/precursor cells as resource in regenerative medicine.

Key words: Chemokine, Fibroblast, Glycosylation, Lectin, Myofibroblast, Stem cell

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Introduction

Operating in different physiological contexts, a bioeffector can underlie diverse outcomes. The detection of this versatility is the starting point for research work with therapeutical perspective. To draw analogies between separate bioprocesses and to trace recurring molecular themes within them are prerequisites to identify routes for application. In this sense, Harold Dvorak's article "Tumors: wounds that do not heal" published nearly 30 years ago was instructive to turn attention to remarkable similarities between the connective tissue reaction in wounds and in cancer. Ensuing work comparing regeneration/wound healing with aspects of malignancy revealed that these two process cascades have even more in common (Smetana et al., 2013a; Rybinski et al., 2014). Owing to the emerging physiological significance of the microenvironment, our review focuses on cells and mediators from this region. They can program cell fate and thus become of interest for controlled manipulations with therapeutic intentions.

Stem cells under physiological conditions and in cancer

A central role in growth/regeneration is played by stem cells. They were first described in the process of hematopoiesis (Loutit, 1968). The following broad-scale research, which even led to founding journals exclusively devoted to this topic, has described their

occurrence, route of differentiation and potential for applications. As to totipotent stem cells, they can be prepared from the early embryo at the stage of several blastomers. Each cell has, as the term 'totipotency' implies, unrestricted capacity to form cell lineages. Pluripotent (embryonic) stem cells are isolated from the embryoblast of a blastocyst, and their daughter cells can practically be differentiated into most types of cells. In contrast to stem cells of prenatal origin, both multipotent stem and progenitor cells are present in the body throughout all periods of life of an organism, and almost all types of tissues harbor their own stem cell pool (Hansis, 2006; Mimeault and Batra, 2006; Yamanaka et al., 2008).

These tissue/adult stem cells are usually located in distinct regions. For example, epidermal and neural crest-originated stem cells reside in the bulge region of the outer root sheath of hair follicles (Sieber-Blum et al., 2004; Blanpain and Fuchs, 2006). They have a very slow rate of proliferation. As a consequence, when labeled by a pulse of radioactive nucleotides, the stem cell pool maintains positivity for a very long period of time (label-retaining cells). When proliferating, their division is asymmetric; this means that the first daughter cell keeps its stem cell properties. In contrast, the second one, the so-called transit-amplifying cell, is the source feeding the differentiation cascade. The transit-amplifying cell rapidly goes through the cell cycle stages to mitosis. The overall number of possible mitotic rounds yet is restricted. Characteristically, these adult tissue stem cells are equipped with protein pumps in their membrane. They efficiently export toxic agents such as xenobiotics from the cytoplasm (Challen and Little, 2006; Mimeaut and Batra, 2006; Inaba and Yamashita, 2012). Hereby, stem cells minimize the risk of damage to their genome. While work with stem cells *in vitro* has been accomplished, it is being noticed that adult tissue stem cells *in vivo* thrive in a special microenvironment. This is called the niche (Watt and Hogan, 2000; Das and Zouani, 2014). A current challenge to further applicability of stem cells is to define the niche's properties in detail.

Malignancies of blood cells are assumed to arise due to aberrations from the regular course of differentiation of bone marrow stem cells. These molecular deviations and their consequences then account for the production of abnormal cells, which are released into circulation. In view of the success rate to graft solid tumor cells to a genetically non-identical donor of the same species, the existence of cells with properties of stem cells had also been proposed for solid tumors (Glinsky et al., 2008; Sell, 2010). Work on teratoma cells supported the concept for tumor stem cells. In fact, when introduced into the cavity of a blastocyst, such cells even took part in forming the embryo and adult animals, with phenotypic properties dependent on the teratoma cell donor (Mintz and Illmensee, 1975; Solter, 2006). These data harmonize well with observations on the fate of embryonic stem cells, which are the source of a teratoma/teratocarcinoma when grafted to the adult host. These findings point to two important conclusions: i) stem cells have potential to become malignant, and ii) the microenvironment has a respective bearing on these rather undifferentiated but genetically normal cells. Further work on different tumor types showed that cancer stem cells can play salient roles in the majority of the tested carcinomas, such as those developing in breast (Owens and Naylor, 2013), prostate (Chen et al., 2013), colon/rectum (Fanali et al., 2014), lung (Singh and Chellapan, 2014), skin (Shakhova, 2014), in the head and neck region (squamous cell carcinomas) (Chovanec et al., 2005; Zhang et al., 2012) and/or in brain (Pointer et al., 2014). It is quite likely that cancer stem cells underlie complications in cancer therapy, especially with respect to minimal residual disease. Here, the cells, which survive tumor therapy, are at the heart of initiating tumor relapse. As a down-side for the success of chemotherapy, these cells can remove cytostatic drugs from their cytoplasm by the efficient transport mechanism mentioned above (Motlík et al., 2007). Having herewith emphasized the relevance of stem cells for onset and propagation of malignancy, it is instructive to next deal with the potential of host factors to affect disease progression.

In this context, the paradigm in tumor biology has shifted from rather exclusively focusing on tumor cells to the microenvironment, with its immune and stromal cells as well as mediator proteins produced by these cell types (de Visser et al., 2006; Le Bitoux and Stamenkovic, 2008; Mbeunkui and Johann, 2009; Grivennikov et al., 2010; Galdiero et al., 2013; McAllister and Weinberg, 2014; Marcucci et al., 2014). In addition to cancer-associated fibroblasts (CAFs), which are frequently positive for α-smooth muscle actin (SMA), and infiltrating leukocytes such as cancer-associated macrophages (CAMs), several biochemical components of the extracellular matrix (ECM) play a role to endow the microenvironment with pro-tumoral properties (Fig. 1) (Plzák et al., 2010; Gatazzo et al., 2014).

Cancer-associated fibroblasts

The origin of CAFs is not yet fully clear. Its ancestry is traced to different sources, one of them epithelial-mesenchymal transition (Petersen et al., 2003; De Wever et al., 2008; Haviv et al., 2009). Another route to CAFs can start from bone marrow-derived mesenchymal stem cells (Mishra et al., 2008; Nishimura et al., 2012). Acting on malignant cells, such stromal cells can significantly stimulate both tumor growth and metastatic behavior (Karnoub et al., 2007) as well as suppress immune recognition of cancer cells (Ling et al., 2014). They are thus considered as "culprits in tumor growth, immunosuppression and invasion" (Stromnes et al., 2014).

Bone and/or cartilaginous metaplasia are also present in malignant tumors such as squamous cell

(Katase et al., 2008) and breast carcinomas (Downs-Kelly et al., 2009). Occurrence of bone or cartilage in tumor stroma is an indicator for the presence of mesenchymal stem cells at this site and reflects their inherent plasticity for differentiation. Interestingly, CAFs isolated from basal cell carcinoma induced expression of transcription factors Oct-4 and Nanog, markers of embryonic stem cells, in co-cultured mouse 3T3 fibroblasts. Moreover, the capacity for differentiation of these 3T3 cells exposed to CAFs then comes close to the plasticity of mesenchymal stem cells (Szabo et al., 2011). These data add support to the growing notion that the stromal part is an active player for tumor biology. Of note, recent work on autochthonous mouse models of pancreatic cancer presenting intraepithelial neoplasia, acinar-to-ductal metaplasia and progression to ductal adenocarcinoma highlighted the possibility for a favorable aspect, i. e. host protection by precluding to let more aggressive tumor cells arise (Oezdemir et al., 2014; Rhim et al., 2014). This evident ambivalence justifies respective research efforts. In their vicinity, CAFs are apparently capable to reprogram cells to let them gain a stem cell-like character. As the test case of pancreatic cancer exemplifies, tumor cells may alternatively acquire a moderate or advanced status of differentiation (Gore and Korc, 2014).

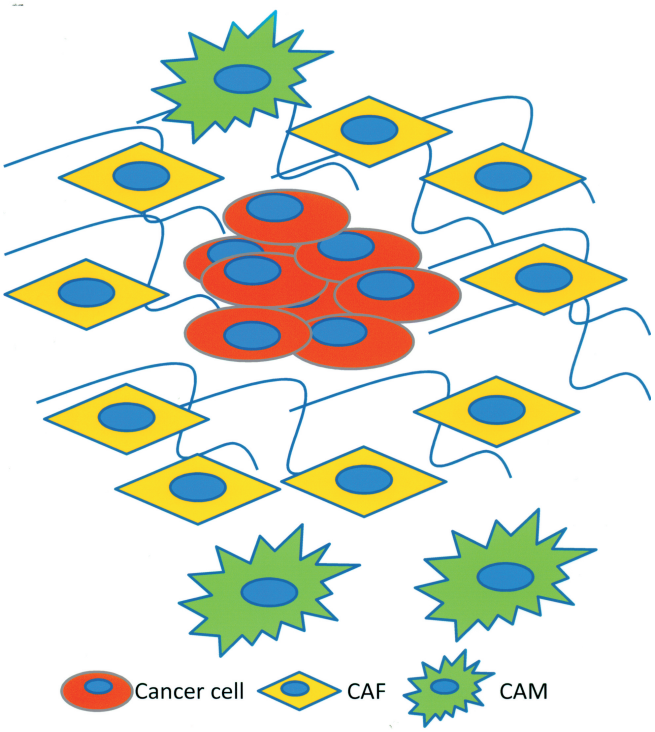

Fig. 1. Cancer-associated fibroblasts (CAFs) and distinct types of leukocytes such as cancer-associated macrophages (CAMs) contribute to establish a micromilieu that supports tumor cell growth and spreading.

In addition to the noted sources, CAFs can develop from fibroblasts of the local mesenchyme (Mueller et al., 2007), *in situ* harboring SMA (Cirri and Chiarugi, 2011). Bioactive fibroblasts, having properties similar to CAFs but without SMA, can also be generated under *in vitro* conditions by co-culture either with carcinoma cells or with normal keratinocytes (Kolář et al., 2012). As will further be discussed below, the pattern of expression of mediator proteins by fibroblasts is drastically altered, in turn changing the micro-environment (Fig. 2). By comparing the activity levels of normal fibroblasts and CAFs isolated from squamous cell carcinoma, one crucial difference was observed: whereas the activation of normal fibroblasts was time restricted, that of CAFs was prolonged to more than four weeks in culture (Szabo et al., 2013).

A key effector for the conversion of local fibroblasts to CAFs is the transforming growth factor-β1 (TGF-β1) (Casey et al., 2008; Brenmoehl et al., 2009). To pinpoint any effect of cancer cells on normal fibroblasts *in vitro*, both cell types were co-cultured. Although cancer cells alone were not able to induce production of SMA in normal dermal fibroblasts, proteomic analysis demonstrated a marked impact of the co-cultured epithelial cells on presence of proteins operative in the cytoskeleton, especially in actin functionality, such as caldesmon-1, cofilin and calponin-2 (Jarkovská et al., 2014). In addition, significant changes in serum levels of mRNA coding for apoptosis/growth-regulatory proteins of the p53 pathway such as p53 itself, p21, cyclin D, MDM2, CASP3, and MAX as well as Bcl-2 family proteins (Bcl-2, Bcl-XL, Bcl2L1, Mcl1, and BclAF1) were observed in patients with head and neck squamous cell cancer (Čapková et al., 2014). Evidently, intercellular communication in this system markedly influenced gene expression poised to reprogram motility and cell growth properties.

Turning back to TGF-β1 and its ability to alter cellular aspects within the microenvironment, a pertinent question was whether other proteins have similar capability. We have recently identified a new class of endogenous factors for CAF generation, i. e. adhesion/growth-regulatory lectins of the galectin family (for review, please see Cooper, 2002; Gabius et al., 2011; Kaltner and Gabius, 2012; Smetana et al., 2013b). Galectins share the β-sandwich fold and a sequence signature with a central Trp residue in the contact site for sugars, preferentially β-galactosides as reflected in the name (Barondes, 1997; Gabius, 1997; Kasai, 1997; Ahmad et al., 2002; Hirabayashi et al., 2002). Like other classes of lectins active extracellularly in cell adhesion and ordered cell migration (Gabius et al., 1985a; Gready and Zelensky, 2009; Schwartz-Albiez, 2009), galectins can serve as bridge between cells or cells and the ECM (Brewer, 1997). Equally important, bi- and oligovalency of galectins is instrumental for cargo selection and transport as well as cluster formation on membranes. For example, N-glycans with N-acetyllactosamine termini guide galectin-4-dependent apical or axonal glycoprotein

routing and status of microdomain integrity is a switch for galectin affinity (Stechly et al., 2009; Kopitz et al., 2010; Velasco et al., 2013), The capacity to read distinct glycan signatures on cellular structures (in terms of structure and topology of presentation) is readily revealed by applying human galectins as tool in cyto- and histochemistry (Gabius et al., 1991; Holíková et al., 2002; Habermann et al., 2011; Kopitz et al., 2013). The target-specific binding, e.g. to glycans of integrins, will induce outside-in signaling. Hereby, galectins elicit diverse cellular responses when binding cell surface glycans, for example mediator release or cell cycle arrest and anoikis/apoptosis (Villalobo et al., 2006; André et al., 2007; Wang et al., 2009). Following their secretion from a cell via a non-classical pathway, they thus become intimately involved in intercellular cross-talk, as the case study on communication between activated regulatory/effector T cells exemplifies with clinical relevance (Wang et al., 2009; Wu et al., 2011a).

Building on its capacity to direct human dermal fibroblasts to the myogenic lineage (Goldring et al., 2002) and also giving heed to its role in tumor promotion by mesenchymal stromal cells (Szebeni et al., 2012), we tested galectin-1. It is a homodimeric protein with contact sites for glycans at opposing sides ideal for cross-linking (López-Lucendo et al., 2004). These assays revealed activity (Dvořánková et al., 2011). It was additive to and independent from that of TGF-β1 (Fig. 3). Thus, this human lectin is a potent elicitor of CAF generation. Because tumors can express a network of galectins, as demonstrated exemplarily for brain, breast, colon, salivary gland, skin and testicular tumors (Gabius et al., 1986; Camby et al., 2001; Kayser et al., 2003; Čada et al., 2009; Saussez et al., 2010; Remmelink et al., 2011; Dawson et al., 2013; for a recent review, please see Gabius and Kayser, 2014), we proceeded to test three further members of this family. Activity was revealed also for galectins-3 (the full-length protein but not its proteolytically truncated form), -4, and 7 (Dvořánková et al., 2011). These proteins belong to the three different subgroups of the galectin family, the non-covalently associated homodimers (galectins-1 and -7), the tandem-repeat-type proteins with two different lectin domains connected by a linker peptide (galectin-4) and the chimera-type galectin-3 with its tail of collagen-like repeats and an N-terminal peptide attached to the lectin domain (Kasai and Hirabayashi, 1996). Together with galectin-1, they often are present in tumors and their stroma, thus likely operative accordingly *in situ*. As consequence, endogenous lectins secreted from tumor cells or produced by stromal cells obviously deserve the same attention as put on growth factors.

Besides the effect on fibroblasts, galectin-1 also stimulates the production of a network of ECM fibers. This is rich in fibronectin, tenascin and galectin-1 itself (Dvořánková et al., 2011; Mifková et al., 2014). For endothelial (HUVEC) cells, the matrix is suited to stimulate proliferation (Perželová et al., 2014). To address the issue on validity of extrapolation from *in vitro* to *in vivo* squamous cell carcinomas of the head and neck were analyzed. This work led to a significant correlation between presence of galectin-1 in tumor stroma and presence of SMA-positive CAFs. Further examining gene expression profiles by microarrays, cancer cells isolated from tumors rich in stromal CAFs and galectin-1 had higher signal intensities for genes implicated in cancer progression such as MAP3K2, TRIM23, PTPLAD1, FUSIP1, SLC25A40 and SPIN1

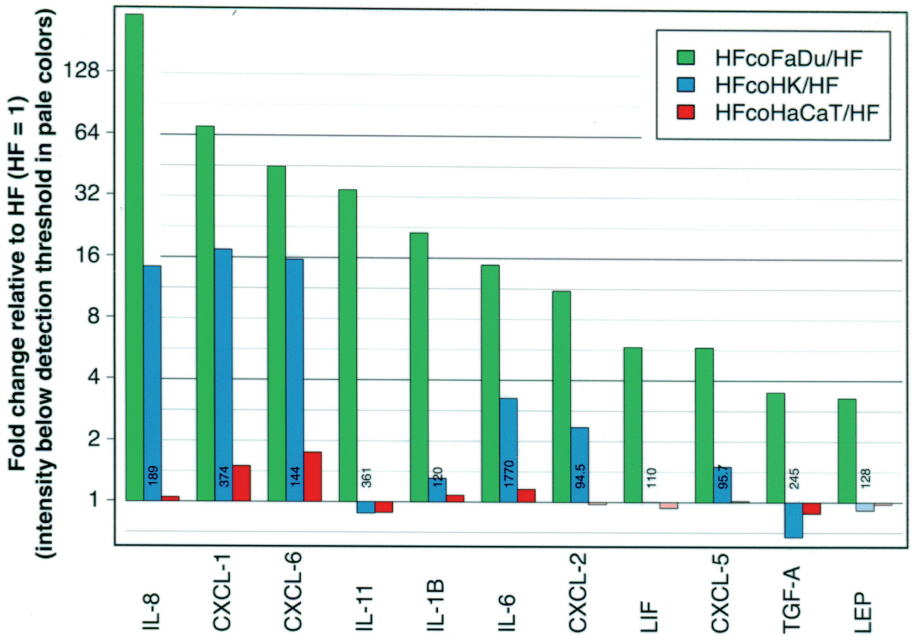

Fig. 2. Markedly elevated expression of genes for chemo- and cytokines as well as growth factors in normal human fibroblasts (HF; set to 1) by co-culture with cells of a squamous cell carcinoma (FaDu) or keratinocytes (K). The same procedure with non-tumorigenic immortalized cells (HaCaT) triggered comparatively minor effects; (kindly provided by Dr. Michal Kolář and Dr. Hynek Strnad from the Institute of Molecular Genetics of the Academy of Sciences of the Czech Republic v.v.i. in Prague).

than preparations from cells isolated from tumors with low levels of the lectin and SMA positivity (Valach et al., 2012). That stromal presence of galectins can be associated with an unfavorable prognosis, as indicated for breast cancer and galectins-1 and -3, respectively (Jung et al., 2007; Moisa et al., 2007), fits into this concept. A rather general role of galectin-1 is indicated when further noting its respective activity in other types of carcinoma, e. g. oral squamous cell carcinoma with impact on SMA positivity, fibronectin/collagen I production and CCL2 presence (Wu et al., 2011b) or pancreatic ductal adenocarcinoma with enhanced Hedgehog pathway signaling in desmoplasia associated to tumor progression (Martínez-Bosch et al., 2014). Concerning the aspect of the age of normal fibroblasts, it is noteworthy that adult cells were found to produce more galectin-1 than foetal fibroblasts (Ho et al., 2014).

Will CAFs affect cell types other than malignant cells? CAFs are also able to even influence normal keratinocytes to acquire a poorly differentiated (tumor-like) phenotype, as we observed in basal/squamous cell carcinomas (Lacina et al., 2007a, b) and in benign tumors, here dermatofibroma (Kideryová et al., 2009). Of note, this phenotype is rather similar to that of epidermal stem or prenatal cells. An effect of stromal fibroblasts had also been noticed in other types of tumors such as malignancies of breast (Casey et al., 2009), pancreas (Hwang et al., 2008) and prostate (Hayward et al., 2001). On the cellular level, marked effects of CAFs on proliferation, epithelial-mesenchymal transition and migration had been reported (Orimo et al., 2005; Fujita et al., 2009; Martin et al., 2010). To contribute to resolve the arising issue on the relationship between the response and the origin of CAFs a comparative analysis was performed in homo- and heterologous systems. Fibroblasts isolated from basal/squamous cell carcinoma and melanoma affected breast cancer cells in a manner similar to that observed by co-culture with fibroblasts isolated from a skin metastasis of breast cancer (Dvořánková et al., 2012). These results indicated that the activity of CAFs will not be strictly tumor-type specific.

In culture and *in situ*, CAFs can act via contacts and also via the production of cytokines/growth factors, proteolytic enzymes and ECM. As noted above, effectors such as lectins are known to act directly on cells or to act

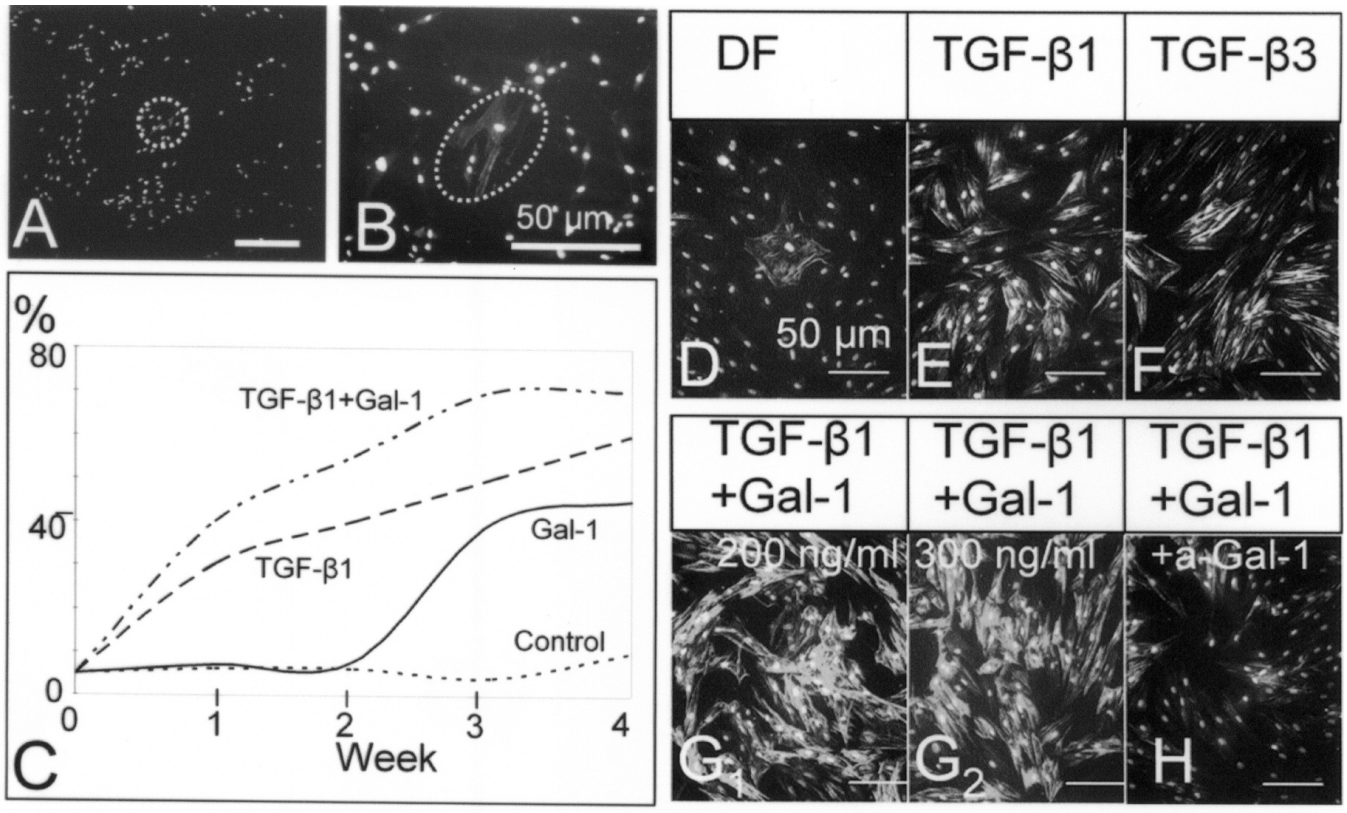

Fig. 3. Extent of occurrence of smooth muscle actin-positive myofibroblasts in control culture of normal human fibroblasts is very low **(A-D)**. Exposure of cells to galectin-1 **(C)**, TGF-β1 **(C, E)** and TGF-β3 **(F)** stimulates generation of these myofibroblasts from normal dermal fibroblasts. Galectin-1 exerts an additive effect to TGF-β1 **(G1, G2)**. Blocking of galectin-1 binding expectably reduces extent of myofibroblast generation. Figure is adopted from Dvořánková et al. (2011), with kind permission of S. Karger AG, Basel.

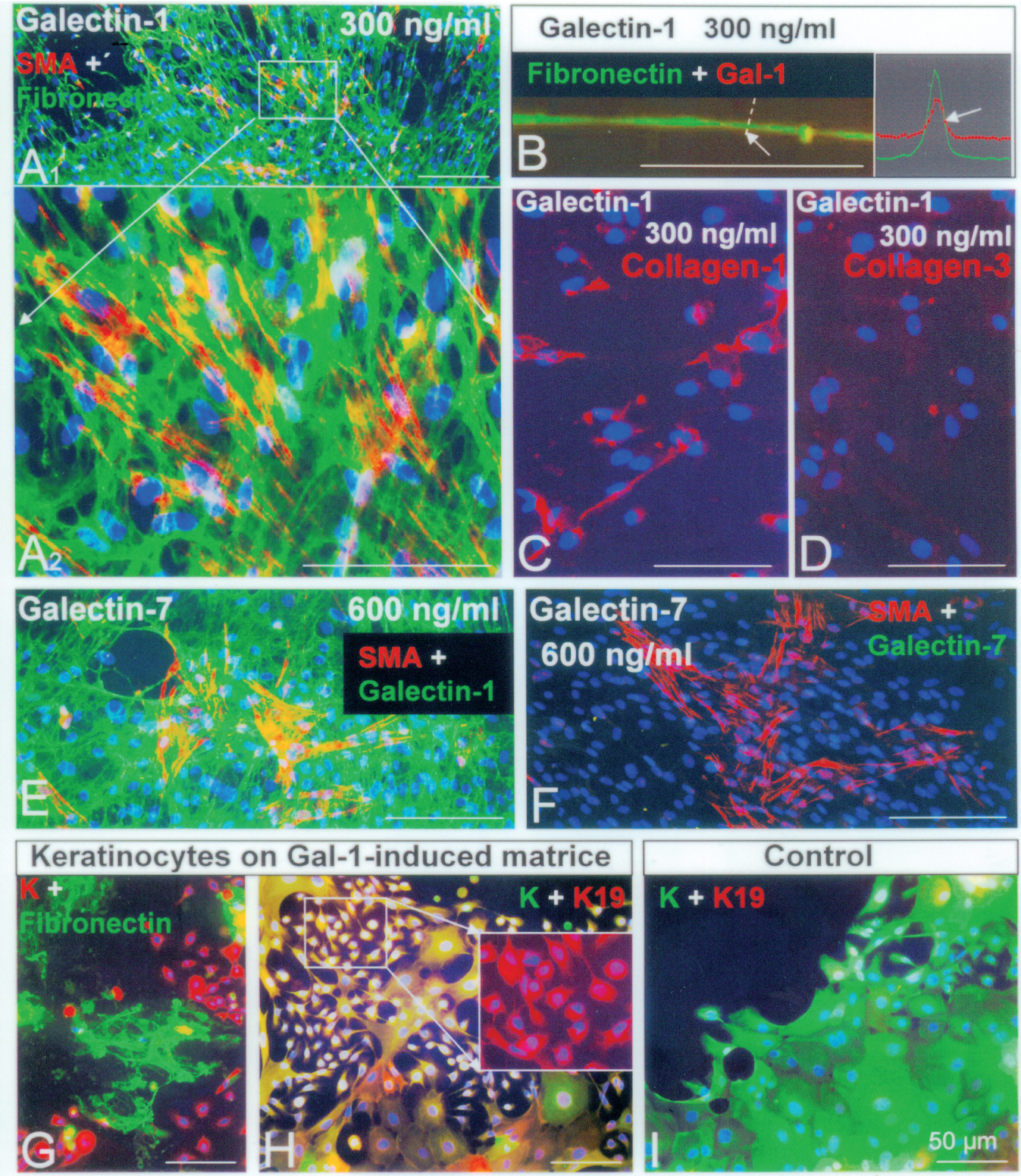

Fig. 4. Galectin-1 stimulates conversion of fibroblasts to smooth muscle actin-positive myofibroblasts **(A1, A2)**. These cells produce a complex network of fibers in the extracellular matrix rich in fibronectin and galectin-1, as demonstrated by the measurement of fluorescence profiles of these two components **(A1, A2, B)**. Production of collagen types 1 and 3 was negligible after the treatment **(C, D).** Besides galectin-1, the proto-type galectin-7 also turns fibroblasts into myofibroblasts **(E)**. Extracellular matrix produced by these cells contained galectin-1 **(E)** but not galectin-7 **(F)**. When this network of extracellular matrix was colonized by human keratinocytes *in vitro*, they actively resorbed this network **(G)**. Of note, these keratinocytes were very small and expressed a marker for low-degree of differentiation status, i. e. keratin 19 **(H)**. Such rather small keratinocytes including keratin 19 positive cells were not observed in classical culture on plastic **(I)**. Figure is adopted from Dvořánková et al. (2011), with kind permission of S. Karger AG, Basel.

as elicitors by induction of cytokines/growth factors (Gabius, 2001; Timoshenko et al., 2010; Ledeen et al., 2012). For example, galectin-3 augments transcription of genes for the chemokines CCL2, 5, 8 and 20 as well as CXCL8 in the range of 3.4-27fold in macrophages (Papaspyridonos et al., 2008) and stimulates production of CCL2, 3 and 5 in synovial fibroblasts suited to recruit mononuclear cells (Filer et al., 2009). These mediators will be discussed further below. That this lectin is a mitogen for fibroblasts and an inducer of collagen I gave reason to link its early on-set expression to failure of hypertrophied hearts (Sharma et al., 2004), broadening clinical correlation.

At this stage, it is also informative to more closely define differences between fibroblast preparations. When comparing gene expression profiles of normal fibroblasts and CAFs isolated from head and neck squamous cell carcinoma by microarrays, differences in nearly 600 genes were observed, among them *IGF2* and *BMP4* appearing as most noteworthy (Strnad et al., 2010). Important growth factors/cytokines produced by CAFs and acting on cancer cells are compiled in Table 1. These factors promote cancer cell proliferation and migration as well as the epithelial-mesenchymal transition, all relevant for progression and spreading of tumor cells from the primary site. To the same outcome, proteolytic enzymes produced by CAFs can likewise be important for epithelial-mesenchymal transitions and tumor progression with spread to distant organs (Stuelten et al., 2005; Orlichenko and Radisky, 2008; Saussez et al., 2009; Taddei et al., 2013). That matrix metalloproteinases (MMPs) -2 and -9 (together with increased filopodia occurrence) in oral squamous cell carcinoma cells and MMP-9 in murine lymphoma and HeLa cells are targets for upregulation by galectins-1 and -7 (Demers et al., 2005; Park et al., 2009; Wu et al., 2009) adds further evidence to the concept of galectin relevance for different effector routes. Matrix degradation by ADAM-15, in contrast, is negatively regulated with galectin-1 presence (Camby et al., 2005).

Turning to the ECM, it represents more than just an inert protection/stabilization scaffold for cells. It is organized either into a complex meshwork of connective tissue or it forms the basement membrane. The structure of the ECM and its composition dynamically reflect functional requirements of tissues, with an intricate balance between matrix production and breakdown by lytic enzymes. Because components of the ECM have been referred to as "Janus-faced" (Tímár et al., 2002), the actual context is a salient factor to foresee functional implications. As proof-of-principle representatives of the ECM in tumors, tenascins-C and W, modular proteins equipped to engage in multiple contacts, were proven to play a major role in the course of tumor growth (Brellier and Chiquet-Ehrismann, 2012), frequently in concert with laminins (Franz et al., 2006). Other ECM constituents that participate in tumor formation are periostin (Tilman et al., 2007) and heparan sulfate proteoglycans (Gomes et al., 2013). The glycosaminoglycan chains of the proteoglycans can serve as a storage place for chemo- and cytokines and growth factors (Buddecke, 2009). Fibronectin in the ECM of malignant tissue, a counterreceptor for galectins via its glycans (André et al., 1999), is able to influence vascularization of tumor stroma (van Obberghen-Schilling et al., 2011). As with the glycans, the three-dimensional architecture of the ECM will likely be pivotal, besides the composition. This topological aspect also works in the interplay of lectins an ECM. Because a commercial matrix (Matrigel) loaded with galectin-1 was highly efficient to present the lectin for inducing apoptosis of activated T cells (He and Baum, 2004), matrix properties can definitely modulate a lectin's *in situ* activity status. Moving from this (glycobiological) secreted effector to cells, the inflammatory cells infiltrating the tumor also deserve proper emphasis.

Inflammatory cells: a double-edged sword

Stimulation of the immune defence, with local infiltration by inflammatory cells, had been faithfully interpreted as favorable indicator, of benefit for patients. By uncovering unsuspected mechanisms, this view has been subject to a paradigmatic change. From the side of the stem cells, their own immunomodulatory properties minimize the risk of their recognition and destruction by defence mechanisms (Maccalli et al., 2014). In addition to such attenuation regulatory T cells, myeloid-derived suppressor cell and CAMs are able to downregulate cancer surveillance and increase the tolerance of the immune system to cancer cells. Toward the same outcome, cells such as CAMs have a strong tumor-supporting effect by locally enhancing the availability of pro-inflammatory (and tumor-stimulatory) cytokines such as interleukin-6, teaming up with CAFs (please see Fig. 2). Of note, TGF-β1, a member of the cytokine

Table 1. Examples of growth factors/cytokines/chemokines produced by CAFs in different types of cancer.

Type of cancer	Growth factor/cytokine/chemokine	Reference
Basal cell cancer	IGF-2, FGF-7, Lep, TGF-β3, GREMLIN	Sneddon et al., 2006; Szabo et al., 2011
Breast	CCL-5, IL-6, IL-8, CXCL-7, CXCL-12, SDF-1	Orimo et al., 2005; Karnoub et al., 2007; Korkaya et al., 2011
Pancreas	TGF-β1–3, BMP-4, FG2-1, FGF-2, FGF-7, FGF-10, HGF, CXCL-12, IL-6, LIF, NGF	Hua et al., 2006; Mahadevan and von Hoff, 2007
Prostate	FGF-2, TNF-α	Kaminski et al., 2006
Squamous cell cancer	IGF-2, BMP-4, IL-6, IL-8, CXCL-1	Strnad et al., 2010; Kolář et al., 2012

family, exerts anti-immune activities (Jackaman and Nelson, 2014; Sideras et al., 2014). Galectin-1 in the tumor stroma, as noted above, may augment immunosuppression by eliciting apoptosis in activated T cells (Pace and Baum, 1997; Smetana et al., 2013b). However, it should be added that suited glycan display can also make tumor cells susceptible to galectin-1-dependent anoikis/apoptosis induction, rendering the activity profile of this multifunctional lectin dependent on the context (Sanchez-Ruderisch et al., 2011; Smetana et al., 2013b). In conclusion, presence of inflammatory cells (and their secreted proteins) has inherent ambivalence precluding immediate and reliable predictions, a challenge for future research. The required monitoring will extend the data basis for allowing to draw analogies to other process cascades.

Wound/tissue healing

As previously highlighted in the seminal paper by Dvorak (1986), numerous cellular events appear to be shared by tumors and wounds, with a successful outcome in wound healing. Looking more closely at skin wound healing, the entire process can be divided into three phases. They cannot strictly be separated from each other (Barbul and Regan, 1993; Reinke and Sorg, 2012): i) inflammatory phase, ii) proliferation phase and iii) maturation/remodeling phase. Broadening its implications, it is justified to apply these three categories to other repair processes, too, for example in striated muscle (Bentzinger et al., 2013). Starting wound healing, clotting of blood and migration of inflammatory cells to the injury site occur. In the acute phase, polymorphonuclear leukocytes (PMNL) establish the demarcation line. It delimits necrotic/damaged tissue from vital parts. PMNL are replaced by tissue macrophages during the chronic phase of inflammation. Approximately two days following the injury, fibroblasts begin to populate the wound, proliferate and produce constituents of the ECM. They also contribute to the microenvironment in terms of its profile of chemo- and cytokines and growth factors (Table 2). Immune cells, predominantly micro- and macrophages, are responsible for removal of tissue debris, and they also protect the wound against infections, mainly by bacteria and fungi. In this defense line, lectins such as galectin-3 (MAC-2 antigen) or the tandem-repeat-type mannose receptor are engaged (Gabius, 2006; Quattroni et al., 2012). Obviously, the term "double-edged sword" fits well to describe the spectrum from beneficial to harmful activities of the local effector panel (Behm et al., 2012). In wound healing, lack of injury-site infiltration by inflammatory cells markedly retards the process (Grim et al., 1988). Fittingly, a poor inflammatory response resulting in a low level of scar formation is observed in neonates and newborns (Bermudez et al., 2011; Borský et al., 2012).

Having described the relevance of SMA-positive CAFs and aspects of galectin functionality, the question arises as to whether equivalent cells and any galectin are an active players of wound healing. Indeed, cellular accumulation in granulation tissue takes place, and galectin-1 reactivity, a prerequisite for activity, has been detected using the human lectin as histochemical tool (Klíma et al., 2009; Gál et al., 2011; Grendel et al., 2012). Using re-epithelialization of rat cornea as model, galectin-3 (and galectin-7 but not galectin-1) was active (Cao et al., 2002; Yabuta et al., 2014). Interestingly, galectin-7 is also implicated in repair following menstruation. Wound cell layers exposed to the lectin (at 2.5 μg/ml) showed transcriptional upregulation of ECM constituents including fibronectin and TGF-β1 (Evans et al., 2014). As then expectable, myofibroblasts positive for SMA are common in skin-wound granulation tissue, TGF-β also belonging to the local inductors secreted from fibroblasts as described for cancer. Due to these cells' contractility they are responsible for wound contraction that effectively reduces the area necessary for re-epithelialization (Werner et al., 2007; Kapoor et al., 2008). An insufficient level of presence of myofibroblasts and/or prolonged inflammation at the wound site can account for extensive scar formation, prompting to consider treatment of wounds with focus on proper functions of fibroblast/myofibroblasts as an attempt to minimize its extent in patients (van Beurden et al., 2005). Interestingly, when compared to skin healing, scarification is significantly reduced in adult oral mucosa, owing to similarities in the healing process seen in neonates (Mak et al., 2009). Combination of all factors mentioned above influences the rate of re-epithelialization in the case of skin wound repair, as it does for proliferation and ensuing differentiation of satellite cells to myoblasts and fusion to muscle fiber in striated muscle repair (Reinke and Sorg, 2012; Bentzinger et al., 2013). Stem or precursor cells, which receive signals for their proper functions from inflammatory cells and fibroblasts, serve as pool and source for the cell material in repair.

Mutatis mutandis, cell generation proceeds similarly in tumors, but terminal differentiation and "wound closure" are not attained (Smetana et al., 2013a). The

Table 2. Examples of main growth factors/cytokines/chemokines involved in wound healing.

Mediator	Producer	Target cell	Reference
VEGF	K, F, MF, E	E, MF	Behm et al., 2012
IGF-2	M, Ch, O	M, Ch, O	Koh et al., 2011
FGF-2	F	K	Peplow and Chatterjee, 2013
TGF-β1–3	K, F, MF, platelets	F, K, MF, E	Behm et al., 2012
IL-1	MF, K, F	E, MF, K, F	Behm et al., 2012
IL-6	F, E, MF, K	E, MF, K	Behm et al., 2012
IL-8	F, K	K, F, E	Gillitzer and Goebeler, 2001
CXCL-1	F, K	K	Gillitzer and Goebeler, 2001

K: keratinocytes, F: fibroblasts, E: endothelial cells, MF: macrophages, M: mesenchymal cells, Ch: chondrocytes, O: osteoblasts

last step of wound healing is represented by the remodeling of connective tissue, the basis of any scar formation. Due to the implications on elasticity its occurrence is physiologically undesirable. Proteolytic degradation and ECM remodeling underlie the reconstitution of the normal status. Again, such processes re-appear in cancer, with different consequences (Behm et al., 2012). If the inflicted damage by wounding is too serious, fibrosis can result. Here, functional cells are replaced by scar-like connective tissue. Fibrosis usually represents the final stage of organ damage with none or only very limited therapeutic perspectives for reversal, myofibroblasts a prominent cell type on the route to its establishment, evocative of their role in cancer (Lopéz-Novoa and Nieta, 2009; LeBleu et al., 2013). With respect to effectors, a galectin (i. e. galectin-3), again, has been delineated to be critically involved in fibrosis, as observed in model studies especially using knock-out mice and looking at heart, kidney, lung and pancreas (Wang et al., 2000; Henderson et al., 2006, 2008; Nishi et al., 2007; Liu et al., 2009; Cullinane et al., 2014). Potentially counterbalancing this profibrotic activity, galectin-9 (at 1-3 μg/ml) significantly increased the percentage of annexin V-positive activated human fibroblasts and was less expressed in patients with idiopathic pulmonary fibrosis (Matsumoto et al., 2013). These observations are indicative for a protective role.

From delineating analogies to envisioning perspectives

The aim of regenerative medicine is to rationally take advantage of the potential of stem cells in therapeutic protocols (Mironov et al., 2004). For example, mesenchymal stem cells can be a resource for correcting defects of the locomotory system (Kuhn and Tuan, 2010). Gaining detailed insights into the way growth factors help to shape a microenvironment suited for stem cell propagation can establish protocols for successful *in vitro* manipulation (Das and Zouani, 2014). Toward this end, ECM properties also come into play, e. g. by favoring growth of human umbilical vein endothelial cells (Perželová et al., 2014) or human keratinocytes. These cells acquired a low level of differentiation as reflected by positivity for keratin 19 (Fig. 4). In this respect, our work on galectins adds protein-carbohydrate recognition to the modes of molecular interactions, whose manipulation can have a therapeutic perspective.

Having been initially detected in malignant cells by haemagglutination in extracts of murine N-18 neuroblastoma cells (Teichberg et al., 1975), then purified by affinity chromatography from murine and human tumors (Gabius et al., 1984, 1985b) and localized in human (breast) tumors immuno-histochemically (Gabius et al., 1986), galectin-1 has become a role model for functional analysis in cancer biology and wound healing. Its presence directs production of a bioactive ECM and myofibroblast generation (Dvořánková et al., 2011), thus inspiring to target this process in tumors by unspecific means (Mifková et al., 2014) or by inhibitors blocking its binding to glycans (Murphy et al., 2013). Synthetic tailoring of the sugar headgroup and of the scaffold for topologically optimal modes of glycocluster preparation up to presentation on glycodendrimersomes are being merged to explore possibilities for selective galectin blocking at high inhibitory potency (André et al., 2003, 2010, 2011, 2012; Percec et al., 2013; Zhang et al., 2014). The controlled (beneficial) activity in wound healing, on the other hand, gives direction to consider protein engineering. Respective ideas for design can either be derived from the study of natural single nucleotide polymorphisms (Ruiz et al., 2014) or from performing systematic mutational re-designing of the lectin site or other regions (Imamura et al., 2011; Kopitz et al., 2014).

Alternatively, learning from physiological regulation of lectin presence, e. g. by metabolites such as butyrate (Katzenmaier et al., 2014), makes molecular switches available. Taking one step further, orchestration of expression of lectins, with intra-network coordination not only seen in tumor but also diseases such as osteoarthritis (Toegel et al., 2014), and of glycans acting as counterreceptors in growth control, e. g. on pancreatic carcinoma cells (Capan-1) *in vitro* by the tumor suppressor $p16^{INK4a}$ which downregulates α2,6-sialylation of the fibronectin receptor to make these cells susceptible to anoikis induction (Sanchez-Ruderisch et al., 2010; Amano et al., 2012), can inspire an innovative approach to make headway with tailoring stem cells to become tools for regenerative medicine (Mironov et al., 2004). Interestingly, the healing process in corneal wounds has a bearing on expression of glycosyltransferases implicated in the synthesis of galectin ligands. Remarkably, enzymes for T antigen synthesis, a ligand for galectin-3 (Krzeminski et al., 2011), are upregulated, that for α2,6-sialylation downregulated (Saravanan et al., 2010). Explicitly, the reprogramming of cell surface glycosylation by altering distinct expression properties of cell surface determinants such as a TGF-β1 receptor (Patsos et al., 2009), and of intracellular proteins such as the Rho GTPase Rac1 also involved in wound healing (André et al., 2014) or by changing a microenvironmental factor of inflammation (NO) (van de Wouwer et al., 2011) can be viewed as means toward regulating susceptibility to tissue lectins. Moreover, at the same time, manipulations of glycosylation can modulate availability of growth factor receptors. Such changes make their presence felt already at the folding stage and/or impair protein stability (Patsos and Corfield, 2009; Zuber and Roth, 2009). In fact, glycosylation then has a bearing on the extent of cell surface presence of glycoproteins, as recently observed for the epidermal growth factor receptor expressed in cell lines deficient in distinct aspects of galactosylation (Gabius et al., 2012).

By letting deciphering the cross-talk between tissue

lectins and their counterreceptors in tumor biology/would healing become a topic of research activity, using techniques from biophysical chemistry to cell biology for analysis (Solís et al., 2014), contributions to advance applicability of the potential of stem/precursor cells can be expected. Also considering tissue lectins as elicitors, e. g. by affecting production and secretion of chemo- and cytokines and growth factors and generating a particular composition of the ECM, shaping of microenvironmental properties can be envisioned. In this sense, monitoring glycan and lectin presence *in situ* has merits beyond a mere status description (Danguy et al., 1994). In view of the unsurpassed capacity of glycans for storing biological information and their emerging significance as versatile signals for diverse bioprocesses (Gabius et al., 2011), exploring this new ground can most likely be very fruitful.

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