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Special issue of *Cell Adhesion & Migration* on Tenascins: Defining their role in tissue homeostasis and cancer

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Since the discovery of its first member, tenascin-C, the tenascin family of extracellular matrix (ECM) glycoproteins is attracting increasing attention. Tenascin-C was first named by Ruth Chiquet-Ehrismann and colleagues in a seminal paper in 1986 (Cell 47, 131). Although this molecule was under investigation concurrently in several laboratories, each of whom bestowed a name that reflected its different function or tissue distribution. Today four family members are known (tenascin-C, -R, -X and -W) that share common domain organization and sequence homologies. Each tenascin is expressed in a tissue and context specific manner with only partial overlap of simultaneous expression with other members, suggesting that each member has a particular non redundant role.

Tenascin-C is found in many developing organs but in the adult is often restricted to specific sites, e.g. around budding or invaginating epithelia (referring to its name: "holding nascent structures"). After birth, tenascin-C expression is reduced to a few tissues with high tensile stress and to places of high cell turnover reminiscent of stem cell niches. During injury, regeneration, and cancer tenascin-C is prominently de novo expressed. Tenascin-R is exclusively expressed in the developing and adult nervous system. Tenascin-X is primarily expressed in skin and muscle tissue, and mutations cause Ehlers Danlos syndrome. Tenascin-W is expressed in kidney, smooth muscle, and most prominently in pre-osteogenic areas in the embryo and periosteum in the adult.

This special issue was inspired by the first international meeting also entitled "***Tenascins: defining their role in tissue homeostasis and cancer***" that was organized by Kim Midwood (University of Oxford, Kennedy Institute for Rheumatology) and Gertraud Orend (University Strasbourg, INSERM U1109) and took place in Strasbourg on 12/13th of May 2014 (**Fig. 1A and B**). This meeting was designed to celebrate and acknowledge the discovery of this exciting family of ECM molecules more than 30 years ago and to bring together researchers in the field from across the world to share data and ideas. At this meeting, 17 invited speakers discussed the newest developments in the specific and common characteristics of tenascin-C, -X -R and -W in evolution, development and tissue homeostasis, as well as in a wide range of diseases over 2 days together with more than 60 participants.

As well as many ideas and collaborations, this meeting also led to the idea to create a ***tenascins webpage*** which is now up and running and can be found at: www.tenascins.org. The aim of this webpage is to provide a forum for the research community to share interest in tenascins, reagents and protocols as well as information about upcoming and past scientific meetings.

In this special issue commissioned by the editor of *Cell Adhesion & Migration*, we have gathered 12 review articles and 2 research papers that reflect the state of the art in the tenascins field. Tenascin-C, as the oldest member of the family, has historically obtained most of the attention of the scientific community, with more than 3000 publications in comparison to publications in the lower hundreds for the other tenascins. This is also reflected in the contributions to this special issue where the majority of articles focus on tenascin-C. However, there is increased, and well deserved, interest in the other family members with exciting new advances continuously emerging. We have tried to reflect this in the issue with one review dedicated entirely to tenascin-X largely covering the knowledge about this exciting molecule, another summarizing what is known about transcriptional regulation of all family members, and another comparative analysis of the role of each tenascin in glioma.

There are few reports documenting mutations in the tenascin genes, raising the question whether there is a selective pressure for preservation of these molecules. So, do we need tenascins and what happens when the organism lacks these molecules? This question has been addressed in murine knockout models and was rather disappointing at the first glance since these mice (tenascin-C, tenascin-R, tenascin-X) had a non-lethal and mostly mild phenotype (except for tenascin-X that phenocopied the Ehler Danlos syndrome). Even knockout of 2 tenascins (tenascin-C/-R) did not show an extraordinary phenotype. Taken into account a recent observation that tenascin-C facilitated elimination of HIV through its interaction with this virus, one could ask the question the other way around, are tenascins crucial for protection against HIV (and potentially other viruses or microorganisms) and therefore have not been discarded during evolution?

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Figure 1. Picture of the participants at the first meeting dedicated to the tenascin family of molecules held in Strasbourg in May 2014.

In this context, we start with a look at tenascin-C through the evolution of species. **Adams** and colleagues describe data which shed new light on how ECM molecules may have co-evolved to modulate the adhesive strength of the ECM in tissues in transition. The fact that tenascin-C evolved before fibronectin raises the provocative question of whether the strongly adhesive fibronectin evolved to counterbalance the anti-adhesive properties of tenascin-C. Moreover, analysis of the RGD integrin binding sequence revealed that in some species (e.g. mouse) tenascin-C lacks RGD, yet tenascin-W has the RGD sequence. This is the opposite in the human genome raising the question whether tenascin-C and tenascin-W might have complementary functions at least in respect to integrin binding.

One defining feature of the tenascins is that, unlike many typically structural ECM components such as fibrillar collagens and fibronectin, these molecules are not ubiquitously expressed, instead exhibiting a very

specific distribution. Moreover, each tenascin family member displays a unique pattern of expression in both tissue specific and temporal manner. Control of tissue levels of these molecules is therefore a key factor in defining tenascin biology. One major mechanism by which this is achieved is via tight transcriptional regulation of tenascin genes. The latest data in this arena are discussed by **Chiovaro** and colleagues, who reveal distinct means of controlling tissue specific expression of different family members.

Tenascins are large molecules in the range of 100-300 kDa for a monomer that form trimers (tenascin-R, -X) or hexamers (tenascin-C, -W). Tenascins are subject to myriad post-transcriptional and post-translational modifications, including alternative splicing, glycosylation, oligomerization and enzymatic cleavage. In this way a wide variety of distinct entities are generated of the same molecule with specific biological functions that are yet all covered by the same family name. **Giblin and Midwood** describe the life cycle of the tenascin-C molecule from transcription to secretion to degradation, detailing how specific modifications along the way control tenascin-C function and how these processes are regulated and mis-regulated during development and tumorigenesis. The expression and modification of tenascins are highly regulated in normal tissue homeostasis and there is good evidence that both are altered in a wide variety of diseases, contributing to disease severity. In this issue **Kasprzycka** and colleagues detail what is known about tenascin-C expression and function in fibrosis, and how these studies can inform new therapeutic approaches to treat fibrotic diseases.

This issue also dedicates a number of articles to the role of tenascin-C in cancer reflecting the explosive progress in our understanding of the contribution of this molecule to poor patient prognosis in numerous different tumors. Some of the mechanisms by which tenascin-C modulates cellular signaling and behavior in the tumor microenvironment are discussed. The modular structure of tenascins confers upon them the ability to bind to a dizzying array of molecules including soluble factors, other matrix resident molecules and cell surface receptors. It is the integration of all this information perceived by the cell that maintains normal tissue homeostasis. The research article by **Spenlé** and colleagues describes the organization of tenascin-C into tracks that can form channels in the murine Rip1Tag2 insulinoma model as well as in human insulinoma and colorectal carcinoma. It is hypothesized that these tenascin-C tracks create local niches with particular mechanical and signaling cues and potentially arise from a genetic program for conduits in the thymus.

Yoshida and colleagues discuss what is known about tenascin-C binding to cell surface integrins and the impact that these interactions have on tumorigenesis. **Shao** and colleagues discuss the potential role of epidermal growth factor (EGF) receptor signaling induced upon binding of the EGFL repeats of tenascin-C in promoting melanoma migration and invasion. **Lowy and Oskarsson** describe molecular mechanisms by which tenascin-C promotes metastasis formation and potentially impacts drug resistance, summarizing clinical data and results from murine models and addressing which isoforms of tenascin-C are expressed in metastatic niches and by which cells. **Berndt** and coauthors summarize our knowledge about synthesis and alternative splicing during carcinoma invasion, and discuss the impact of tenascin-C on disease progression with focus on urothelial carcinoma of the urinary bladder and oral squamous cell carcinoma. In the review by **Brösicke and Faissner** the authors discuss the potential relevance of all four tenascin family members in gliomas. Although tenascin-R, -W and -X are also expressed in glioma little is known about their functional relevance in glioma progression. This is different to tenascin-C on which a detailed summary is provided describing the nature of the expressed tenascin-C isoforms and their potential role in triggering specific signaling involving integrins with relevance to proliferation, migration and angiogenesis.

Its particular high expression in cancer tissue renders tenascin-C an attractive target for anti-cancer intervention therapies. In the review by **Spenlé** and colleagues the authors discuss opportunities of how tenascin-C expression in cancer tissue could be exploited for targeting cancer. They summarize current strategies involving interference of tenascin-C expression as well as using abundance of tenascin-C in the tumor tissue as address for delivery of molecules that are either cytotoxic or attract the immune system to eradicate the tumor. It is also addressed how radiotherapy as the most frequent anti-cancer treatment induces tenascin-C and what impact that could have on tumor relapse. Exemplifying this, **Catania** and colleagues present data from the first phase 1b/II clinical trial of a single chain antibody against the D domain of tenascin-C coupled to IL2 (F16-IL2) in combination with doxorubicin in patients with solid tumors and metastatic breast cancer. In this study, toxicity was controllable and reversible, moreover, combination treatment showed preliminary signs of anti-cancer activity. Altogether, these results are promising and a good basis for future studies on the safety and activity of F16-IL2 in combination with approved anti-tumor drugs.

Tenascin-X is comprehensively reviewed by **Valcourt** and colleagues. Its structural role in matrix assembly and collagen maturation/deposition as well its newly identified function in activating TGFβ signaling is described. Moreover its ying and yang function in regulating epithelial and mesenchymal characteristics is discussed. Finally it is also reviewed how tenascin-X expression compares to tenascin-C in melanoma and other cancers where both molecules may have opposite functions.

Together, the compiled articles in this special issue provide an update on many aspects of the tenascin family of ECM molecules. This knowledge is not only potentially important for diagnosis and prognosis of diseases such as chronic inflammatory diseases, heart disease and cancer but also may feed research for the design of biomaterials for specific purposes including tissue regeneration as recently has been exploited for tenascin-C. In the coming years we expect to gather a better understanding of the function of all tenascin family members that may be discussed at the next meeting dedicated to this exciting family of molecules.