Inflammatory stress and sarcomagenesis: a vicious interplay

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Abstract Chronic inflammation represents one of the hallmarks of cancer, but its role in sarcomagenesis has long been overlooked. Sarcomas are a rare and heterogeneous group of tumors of mesenchymal origin accounting for less than 1 % of cancers in adults but 21 % of cancers in the pediatric population. Sarcomas are associated with bad prognosis, and their management requires a multidisciplinary team approach. Several lines of evidence indicate that inflammation has been implicated in sarcomagenesis leading to the activation of the key transcription factors HIF-1, NF- κ B, and STAT-3 involved in a complex inflammatory network. In the past years, an increasing number of new targets have been identified in the treatment of sarcomas leading to the development of new drugs that aim to interrupt the vicious connection between inflammation and sarcomagenesis. This article makes a brief overview of preclinical and clinical evidence of the molecular pathways involved in the inflammatory stress response in sarcomagenesis and the most targeted therapies.

Keywords Sarcoma · Inflammation · Epidemiology · Genetics · Therapy · Signaling pathways

Introduction

Chronic inflammation has emerged as one of the hallmarks of tumors, but its role in sarcomagenesis has long been overlooked. Already in the nineteenth century, Rudolf Virchow postulated a connection between chronic inflammation and cancer and distinguished sarcomas from carcinomas. The impact of chronic inflammation on sarcomagenesis was

demonstrated almost half a century later by Francis Harbitz. Epidemiological and experimental studies now provide evidence that cancer development is indeed attributed to inflammation. Nowadays, it is generally accepted that up to 25 % of human malignancies are related to chronic inflammation and to microbial and parasitic infections (Colotta et al. 2009; Mantovani 2010; Multhoff et al. 2012; Kundu and Surh 2012; Balkwill and Mantovani 2012; Candido and Hagemann 2013). Chronic inflammation causes an imbalance of the cellular homeostasis commonly designated as the cellular stress response (CSR). Among others, CSR is involved in any stage of tumorigenesis such as initiation, promotion, and progression (Herr and Debatin 2001). It also contributes to chronic inflammation that in turn represents one of the factors conditioning tumor progression (Arlt and Schafer 2011). The major players in CSR are undoubtedly molecular chaperones and heat shock proteins (HSPs; Henderson and Pockley 2005). As summarized by Macario and Conway de Macario (2007), chaperones/HSPs have been critically implicated in carcinogenesis in various ways, and consequently certain forms of cancer may be considered “chaperonopathies”—pathological conditions in which chaperones become etiological and/or pathogenic factors—“by mistake or collaborationism.”

Inflammation also plays a pivotal role in sarcomagenesis. Classical inflammation-associated sarcomas comprise Kaposi sarcoma (KS) and the malignant fibrous histiocytoma (MFH). The latter was historically subdivided into five types: (1) storiform-pleomorphic, (2) myxoid, (3) giant cell, (4) inflammatory, and (5) angiomatoid (for a review see Matushansky et al. 2009; Henderson and Hollmig 2012). Storiform-pleomorphic MFH is typically composed of spindle cells and polygonal/rounded cells, while myxoid MFH harbors a prominent vacuolated matrix. Giant cell MFH is characterized by the presence of multinucleated giant cells with osteoclast features, whereas angiomatoid MFH bears oval to round eosinophilic or spindle-shaped cells with slight pleomorphism.

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An intense inflammatory cell infiltrate composed of histiocytes, lymphocytes, and neutrophils represents the histological hallmark of inflammatory MFH. The expression of cytokines in inflammatory MFH may account for the local inflammatory cell infiltration and the aggressive nature of the malignant cells (Melhem et al. 1993). The inflammatory process is driven by hypoxia-inducible factor 1 (HIF-1; Koga et al. 2005) critically involved in genetic destabilization, angiogenesis, invasion, survival, and growth of tumor cells (Multhoff et al. 2012). In MFH patients, 8-nitroguanine, a product of nitrative DNA damage induced by reactive oxygen species (ROS) and reactive nitrogen species, can be detected in the nuclei of tumor cells and inflammatory cells in tumor tissues, while HIF-1 α , the oxygen-regulated subunit of HIF-1, is expressed in the cytoplasm and nuclei of tumor cells (Hoki et al. 2007b). Apart from HIF-1 α , inducible nitric oxide synthase, nuclear factor-kappa B (NF- κ B) and prostaglandin H₂ synthase 2 (PGHS-2) have been found to colocalize with 8-nitroguanine in MFH tissues and to negatively correlate with the survival indicating an NF- κ B-driven sarcomagenesis (Hoki et al. 2007a, b).

KS is a chronic inflammation-associated malignancy arising from the initial infection of an appropriate endothelial or progenitor cell by Kaposi sarcoma-associated herpesvirus (KSHV; Cancian et al. 2013). Cellular hallmarks of KS progression include hyperproliferation of KSHV-infected cells and infiltration of immune modulatory cells into KS lesions leading to chronic inflammation, angiogenesis, and tumor growth (Douglas et al. 2010). Recent evidence has pointed to the involvement of the NF- κ B pathway in both, KSHV biology and KS pathogenesis (Keller et al. 2006). The inflammatory response generated is thought to attract infected cells and exacerbate the oncogenic properties of the viruses (Rubin and Stiller 2002). Progression of KS depends on a poorly understood interplay between KSHV and the host immune system facilitating the manifestation of a tumor-promoting environment (Douglas et al. 2010).

Epidemiology and genetics

Sarcomas represent an uncommon heterogeneous group of rare human malignancies with diverse pathologically and clinically overlapping features, accounting for less than 1 % of cancers in adults but 21 % of cancers in the pediatric population (Lahat et al. 2008). They can be split up into dozens of histological categories and can occur in virtually any anatomic site. According to the “Surveillance of Rare Cancer in Europe” project, sarcomas can be roughly grouped into soft tissue sarcoma (STS), bone sarcoma (BS), and gastrointestinal stromal sarcoma (GIST; Stiller et al. 2013). The epidemiology of sarcomas is comparable in Europe and the USA. In Europe, the crude incidence is 5.6 per 100,000 per year with 28,000 new cases a year (Stiller et al. 2013).

STS is the most frequent sarcoma entity (85 %) followed by BS, the latter accounting for 14 % of all sarcomas. Chondrosarcoma (CS) and osteosarcoma (OS) are the most frequent malignant bone tumors, accounting for more than half of all BS diagnoses. Liposarcoma (LS), leiomyosarcoma (LMS), fibrosarcoma (FS), and MFH represent the most common histologic subtypes of STS. Incidence rates increase with age (Toro et al. 2006), and younger STS patients (<50 years) have significantly better survival than older patients (Ferrari et al. 2011). Several inherited disorders predispose to sarcoma development including Li-Fraumeni syndrome, neurofibromatosis type 1 (at risk for malignant peripheral nerve sheath tumors and GIST), familial adenomatous polyposis (at risk for intraabdominal desmoids tumors), and Baller-Gerold syndrome (Table 1). Patients with RAPADILINO syndrome, Diamond-Blackfan anemia, Rothmund-Thomson syndrome, Werner syndrome, and Bloom syndrome are at high risk of developing OS (Calvert et al. 2012; Suhasini and Brosh, Jr. 2013). Other risk factors include heterozygous germline mutations in the fumarate hydratase gene predisposing to hereditary leiomyomatosis and renal cell cancer (HLRCC; Tomlinson et al. 2002). HLRCC tumors overexpress HIF-1 α and its targets such as vascular endothelial growth factor (*VEGF*) accompanied by a higher microvessel density (Pollard et al. 2005). In patients with familial GIST, activating mutations in the genes of stem cell factor receptor c-Kit and platelet-derived growth factor receptor alpha (PDGFR- α) have been identified (Heinrich et al. 2003), culminating in blockage of apoptosis and cell proliferation, respectively (Rubin et al. 2007). Moreover, single nucleotide polymorphisms (SNPs) in certain genes such as Mdm-2 (*MDM2*), insulin-like growth factor receptor 2 (*IGF2*), and Fas protein (*FAS*) have been found as being associated with increased risk of OS (Savage and Mirabello 2011). SNPs affect many biological effects including upregulation of the negative p53 regulator Mdm-2 and inhibition of the p53 signaling pathway, thereby promoting tumor formation (Bond et al. 2004).

The chromosomal *EWS/FLI1* translocation is a defining characteristic of Ewing’s sarcoma (ES) forming oncogenic fusion transcripts and proteins. The chimeric proteins commonly represent artificial transcription factors dysregulating gene expression and consequently modifying growth and differentiation processes leading to cell transformation due to their oncogenic potential (Ross et al. 2013). *EWS/FLI1*-regulated target genes include the Src tyrosine kinase *LYN*. Targeting Lyn using siRNA or the pharmacological inhibitor AP23994 suppressed tumor growth, decreased bony lysis, and lowered lung metastases in an ES xenograft tumor model (Guan et al. 2008). Elevated Lyn kinase activity was recently demonstrated in numerous KS and glioblastoma patient samples (Prakash et al. 2005; Stettner et al. 2005) suggesting that Lyn plays a seminal role in promoting the malignant phenotype in these cancers and further supporting the consideration

Table 1 Inherited cancer predisposition syndromes associated with increased rates of sarcoma

Disorder	Chromosome	Gene, protein	Function	Sarcoma associated
Baller-Gerold syndrome	8q24.3	<i>RECQL4</i> , RecQ protein-like 4	DNA helicase	OS
Bloom syndrome	15q26.1	<i>BLM</i> , RecQ protein-like 3	DNA helicase	OS
Diamond-Blackfan anemia	Multiple	<i>RPS19</i> , <i>RPL5</i> , <i>RPL11</i> , <i>RPL35A</i> , <i>RPS7</i> , <i>RPS17</i> , <i>RPS24</i>	Ribosomal proteins S19, L5, L11, L35a, S7, S17, S24	OS
Familial adenomatous polyposis	5q21	<i>APC</i> , adenomatous polyposis coli	Tumor suppressor, cell migration, cell adhesion, chromosome segregation, spindle assembly, apoptosis, neuronal differentiation	intraabdominal desmoids tumors
Familial GIST syndrome	4q12	<i>CKIT</i> , c-Kit (CD117) <i>PDGFRA</i> , PDGFR- α	Stem cell factor receptor, protooncoprotein Platelet-derived growth factor receptor alpha	GIST
Hereditary leiomyomatosis and renal cell cancer (HLRCC) syndrome	1q43	<i>FH</i> , fumarate hydratase (fumarase)	Krebs cycle enzyme, tumor suppressor	Leiomyomas and leiomyosarcomas of the skin and uterus in combination with papillary renal cell cancer
Li-Fraumeni syndrome	17p13.1	<i>TP53</i> , tumor suppressor p53	DNA repair, apoptosis induction	OS, STS
Neurofibromatosis type 1 (<i>syn.</i> von Recklinghausen's disease)	17q11.2	<i>NF1</i> , neurofibromin	Tumor suppressor, stimulation of protooncoprotein p53	Malignant peripheral nerve sheath tumors, GIST
RAPADILINO syndrome	8q24.3	<i>RECQL4</i> , RecQ protein-like 4	DNA helicase	OS
Retinoblastoma	13q14.2	<i>RBI</i> , retinoblastoma 1	Tumor suppressor, cell cycle control,	OS, STS
Rothmund-Thomson syndrome	8q24.3	<i>RECQL4</i> , RecQ protein-like 4	DNA helicase	OS
Werner syndrome	8p12	<i>WRN</i> , RecQ protein-like 2	DNA helicase	OS

of Lyn as being a potential therapeutic target for the treatment of certain sarcoma subtypes.

Pathobiology

Ras/Raf/MAPK, PI3K/AKT/mTOR, c-Met

Several crucial signaling pathways have been identified in sarcomagenesis. These pathways include the Ras/Raf/MAPK (mitogen-activated protein kinase) cascade, the PI3K (phosphatidylinositol 3-kinase)/AKT/mTOR (mammalian target of rapamycin) pathway, Notch, sonic hedgehog (Hh), and the receptor tyrosine kinase (TK) c-Met with its ligand, hepatocyte growth factor (HGF). Commonly, c-Met is expressed by epithelial and mesenchymal cells and regulates several cellular responses such as cell proliferation, survival, motility, invasion, and morphogenesis. The c-Met/HGF pathway represents one of the most frequently dysregulated pathways in human cancers with aberrant signaling found in most solid tumors and hematological malignancies. Amplification or overexpression of c-Met has been demonstrated in OS and MFH (Lahat et al. 2011). As given in Fig. 1, growth factor-induced activation and/or receptor overexpression, amplification, or mutation induces

multiple downstream effector molecules and cascades including Ras/Raf/MAPK, PI3K/AKT/mTOR, and STAT-3/-5 (signal transducer and activator of transcription 3/5; Liu et al. 2010). This triggers a number of mitogenic processes promoting cell survival and proliferation, and upregulating antiapoptotic signals and cell cycle proteins (Takebe et al. 2011). Hyperactivation of mTOR in humans can also be achieved by inactivation of the tumor suppressor gene *PTEN*, lack of the tumor suppressor kinase Lkb-1, and loss of inhibitory function of tuberous sclerosis complex proteins (Yang and Guan 2007).

Protooncogene activation represents a critical component in cancer-related inflammation. In this context, mutations in *RAS* genes play an important role in sarcomagenesis with activating *RAS* mutations found in up to 44 % of human STS (Yoo et al. 1999) and in up to 35 % of human embryonal rhabdomyosarcoma (RMS; Martinelli et al. 2009). In tumor cells, activation of mutated Ras is followed by induction of several intracellular signaling pathways including the Raf/MEK (mitogen-activated protein kinase kinase)/ERK (extracellular signal-regulated protein kinase) cascade, the PI3K/AKT/mTOR pathway, and RalGDS proteins (Downward 2009). RalGDS comprise a family of nucleotide-exchange factors activating small GTPases such as RalB followed by activation of interferon regulatory factor (IRF) 3/-7 and

Fig. 1 Signaling pathways involved in sarcomagenesis. Growth factor-induced activation and/or overexpression, amplification, or mutation of receptor tyrosine kinases such as c-Met, c-Kit, VEGFR, IGF-1R, and PDGFR leads to recruitment of adaptor proteins including Grb-2 (growth factor receptor-bound protein 2), GAB-1/2 (Grb2-associated binding protein 1/2), and IRS (insulin receptor substrate) and induces multiple downstream effector molecules such as FAK (focal adhesion kinase), MEK (mitogen-activated protein kinase kinase), ERK (extracellular signal-regulated protein kinase), Rheb (Ras homolog enriched in brain), c-Src, Shc (Src homology 2 domain-containing transforming protein), Shp-2 (Src homology 2 domain-containing tyrosine phosphatase), and Sos (son of sevenless) as well as signal transduction pathways including Ras/Raf/MAPK (mitogen-activated protein kinase), PI3K (phosphatidylinositol 3-kinase), AKT, and STAT-3/5 (signal transducer and activator of transcription 3/5). This triggers several cellular processes modifying cytoskeleton arrangement and promoting cell proliferation, survival, motility, invasion, and adhesion

NF- κ B. NF- κ B not only functions as a crucial regulator of inflammation, cell survival, and immune responses but also participates in cellular transformation and tumorigenesis. In cancer cells, a constitutive activation of this pathway, via chronic RalB activation, restricts apoptosis initiation after oncogenic stress (Chien et al. 2006). Furthermore, IRF-3 and IRF-7 activation induces production of proinflammatory and growth-promoting mediators (Hacker and Karin 2006). Oncogenic K-Ras is a direct inducer of proinflammatory interleukin (IL) 6 and IL-8 required for initiation of tumor-associated inflammation and neovascularization (Sparmann and Bar-Sagi 2004; Ancrile et al. 2007). Targeting NF- κ B signaling pathways might thus be effective in treating Ras-mutated tumors. Interestingly, NF- κ B inhibition by dehydroxymethylepoxyquinomicin inhibited proliferation, decreased mitotic index, and triggered apoptosis of OS cells (Castro-Gamero et al. 2012), while the semisynthetic flavonoid 7-mono-O-(β -hydroxyethyl)-rutoside potentiated the antitumor activity of doxorubicin in human LS cells (Jacobs et al. 2011).

IGF, sonic hedgehog, Notch

One of the major pathways involved in sarcomagenesis is the insulin-like growth factor (IGF) system. Receptor ligation by IGF-1/2 creates multiple docking sites for the adaptor proteins insulin receptor substrate (IRS) 1/2, and Shc. IRS-1 and IRS-2 binding results in successive activation of PI3K, AKT, and the mTOR-containing complex mTORC-2 (Guertin and Sabatini 2005). AKT activation exerts antiapoptotic effects through inhibition of proapoptotic factors (Bad, Foxo) and upregulation of antiapoptotic proteins (Bcl-2, Bcl-x_L, NF- κ B; Datta et al. 1999). AKT signaling also impacts glucose metabolism, protein synthesis, and cell growth by regulating the activity of the mTORC-1 complex (Efeyan and Sabatini 2010). In contrast, Shc binding to activated IGF-1 receptor (IGF-1R) activates the Ras/Raf/MAPK pathway, and induces transduction of mitogenic signals (Pollak 2008). An upregulated expression of IGF-1/2 or IGF-1R has been identified in various sarcomas such as synovial sarcoma (SS), RMS, LMS, OS, and GIST (Quesada and Amato 2012). SS exhibits characteristic t(X;18) translocations

that result in enhanced transcription of the *IGF2* gene, hyperactivation of IGF-1R, AKT phosphorylation, and p44/42 MAPK activation (Friedrichs et al. 2008). The characteristic *EWS/FLI1* translocation in ES upregulates IGF-1 and downregulates IGF binding protein 3, enabling an autocrine regulatory loop between IGF-1 and IGF-1R, which can be interrupted by IGF-1R targeting agents (Scotlandi et al. 2002; Prieur et al. 2004). Preliminary clinical data argue for a link between members of the IGF system to increased cancer risk and pathological alterations in sarcomas (Zha and Lackner 2010).

A wide range of prosurvival factors are activated by the essential embryonic sonic hedgehog (Hh) signaling pathway. Aberrant activation of this pathway has been reported for RMS, OS, CS, and ES (Martin Liberal et al. 2012). Upon Hh activation, upregulated expression of several marker genes (e.g., *PTCH1*, *GLI1*, *GLI3*, *MYF5*) can be observed in embryonal RMS and in fusion gene-negative alveolar RMS (Zibat et al. 2010). Recent observations suggest a contribution of the serine/threonine kinase Mirk to the Hh pathway in sarcomas. Mirk is a downstream effector of oncogenic K-Ras and an active kinase in RMS and OS cells (Jin et al. 2007). It is highly expressed in OS, uterine sarcoma, CS, SS, and ES (Yang et al. 2010). Since Mirk has been found to enhance Gli1-dependent gene transcription and to act synergistically with sonic Hh in inducing transcription, Friedman (2011) hypothesized that Mirk alters Hh signaling and consequently controls the stromal environment of these tumors. Together with the finding of an elevated Hh signaling in cancer stem cells and nonmalignant stromal cells surrounding malignant tumors, the Hh pathway can be considered as key cofactor in sarcomagenesis (Takebe et al. 2011). Interestingly, the aggressiveness of RMS and OS appears to be related to the Notch pathway (Tanaka et al. 2009; Roma et al. 2011). Members of the Notch family are highly conserved transmembrane receptors affecting proliferation and apoptosis of diverse cell types. An abnormal upregulation of the Notch pathway has been found in SS, medulloblastoma, and neuroblastoma acting as a prosurvival and proangiogenic factor (Fan et al. 2006; Francis et al. 2007; Funahashi et al. 2008).

Osteopontin, angiogenin

In addition to the classical tumor-promoting molecules such as cytokines, chemokines, and matrix-degrading enzymes, the matricellular protein osteopontin (OPN) was identified as a key player in inflammation and tumor progression. An upregulated OPN expression occurs in 90 % of patients with highly aggressive glioblastoma (Atai et al. 2011). Herein, OPN colocalized with neutrophils and macrophages implying that OPN promotes migration of cancer cells and leukocytes in tumors. High OPN expression correlates with poor prognosis in cancer patients. In STS, elevated OPN levels in serum and

tumor tissues coincide with clinical parameters and function as an important negative prognostic factor (Bache et al. 2010). In female STS patients and those who received curative radiotherapy, high expression levels of *OPN* splice variants were determined as negative prognostic and predictive markers (Hahnel et al. 2012). Upregulation of certain *OPN* splice variants could also be demonstrated in malignant mesothelioma (MM) peritoneum specimens (Ivanov et al. 2009). Despite its cell migration stimulating capacity, OPN mediates cell adhesion and survival of many cell types (Lund et al. 2009). OPN signals via the cell surface receptor RAGE (receptor for advanced glycation end products) and $\alpha\beta3$ -integrin leading to upregulation of NADPH oxidase and concomitant raise in ROS levels. This culminates in activation of AKT, MAPKs, and NF- κ B regulating the expression of several growth-promoting genes involved in cell survival, angiogenesis, and metastasis (Kundu and Surh 2012). Notably, stimulation of human CS cells with OPN increased expression of invasiveness- and angiogenesis-promoting matrix metalloproteinase (MMP)-9 via activation of focal adhesion kinase (FAK), MEK, ERK, and NF- κ B (Chen et al. 2009). Further evidence for the proangiogenic role of OPN is provided by the finding that OPN enhances tumorigenesis and angiogenesis of murine neuroblastoma cells in mice rendering OPN a promising target in sarcoma therapy (Hirama et al. 2003).

Angiogenin (ANG), a 14-kDa multifunctional proangiogenic growth factor, is upregulated in several types of sarcoma including OS and ES (Kushlinskii et al. 2000), alveolar soft part sarcoma (ASPS; Lazar et al. 2007), and KSHV-associated cancers such as KS (Sadagopan et al. 2009). ANG plays a crucial role in the antiapoptotic state of KSHV-infected cells by suppressing p53 functions (Paudel et al. 2012). Moreover, ANG expression inhibits proapoptotic Bax and p21^{Waf-1} expression, induces antiapoptotic Bcl-2, and blocks cell death (Sadagopan et al. 2012). ANG colocalized with the p53 regulator protein Mdm-2 and increased p53/Mdm-2 interactions, suggesting that ANG promotes p53 inhibition thereby mediating antiapoptosis and cell survival (Sadagopan et al. 2012). ANG upregulation can therefore be considered as a crucial player in inflammation-associated tumorigenesis of certain sarcomas. Apart from ANG, KSHV infection upregulates several host genes involved in angiogenesis such as *VEGF* and *PGHS2* (Sivakumar et al. 2008; Sharma-Walia et al. 2010). KSHV induced robust *PGHS2* expression and prostaglandin E₂ (PGE₂) secretion during primary infection of human microvascular endothelial cells and foreskin fibroblasts (Sharma-Walia et al. 2006). KSHV infection-induced *PGHS2*/PGE₂ expression also upregulated Rac1-GTPases in adhering endothelial cells thereby accelerating cell adhesion. Furthermore, KSHV infection-induced *PGHS2* modulated survival, proliferation, and angiogenesis of latently infected endothelial cells by inducing secretion of numerous growth (PDGF-BB, IGF-1, granulocyte colony-stimulating factor (G-CSF), IL-8), angiogenesis (VEGF, ANG,

oncostatin, IL-8, MMP-2), inflammation (IL-1, tumor necrosis factor (TNF), RANTES, IL-8) and invasiveness-promoting factors (MMP-2/-9).

Micro-RNAs

The discovery of micro-RNA (miRNA) identified this RNA subtype as a crucial player in linking inflammation with cancer causation. The knowledge of miRNA expression patterns in cancer may have substantial value for diagnostic and prognostic determinations as well as for therapeutic intervention. miRNAs are a class of small RNAs that posttranscriptionally regulate gene expression critically involved in transformation differentiation, and proliferation. Global alterations in miRNAs can be observed in a number of disease states including cancer. A comprehensive analysis of miRNA expression profiles of 27 sarcomas identified distinct miRNA expression profiles among the tumor types (Subramanian et al. 2008). In GIST, the observed downregulation of miR-221 and miR-222 was suggested to facilitate increased translation of *CKIT* thereby enhancing its oncogenic potential. Significant overexpression of miR-1, miR-133a, and miR-133b was found in LMS playing a major role in myogenesis and myoblast proliferation. In contrast, several groups demonstrated a strikingly decreased expression of miR-1 and miR-133a in alveolar and embryonal RMS cells (Yan et al. 2009; Rao et al. 2010). In SS, miR-143 was expressed at very low levels relative to GIST and LMS, whereas in alveolar RMS, high levels of miR-335 can be found (Subramanian et al. 2008). From these data, one can speculate that the clearly distinct miRNA expression signatures among the tumor types studied might implicate their role in tumorigenesis in these cancers and their potential as diagnostic markers or even therapeutic targets. The forced re-expression of miR-206 in RMS cells prevented xenograft growth in vivo by targeting the mRNA of the oncogenic c-Met receptor (Yan et al. 2009; Taulli et al. 2009). Moreover, re-expression of miR-1 or miR-206 blocked human RMS growth in xenotransplanted mice (Taulli et al. 2009). Since c-Met is a direct miR-206 target in RMS, the miR-206-dependent posttranscriptional inhibition of c-Met expression markedly contributes to the antitumor effects of this miRNA rendering tissue-specific miRNAs as holding great therapeutic potential. In LS cells, miR-155 has been shown to be the most overexpressed miRNA and its knockdown blocked tumor growth in murine xenografts (Zhang et al. 2012). miR-155 is also upregulated in endometrial carcinosarcoma (ECS) which is known to undergo a true epithelial to mesenchymal transition (EMT). Castilla et al. (2011) demonstrated that the loss of epithelial characteristics, including cadherin switching and the acquisition of a mesenchymal phenotype, was accompanied by changes in the profile of miRNA expression and an upregulation of E-cadherin repressors analyzed. These data suggest that in human ECS, the interplay between transcriptional repressors of E-cadherin and miRNAs

provides a link between EMT activation and the maintenance of stemness. Of note, inflammatory mediators such as TNF, IL-1 β , IL-6, IL-8, and LPS are able to upregulate miR-155 in cancer cells. miR-155 increases the proliferation of adenocarcinoma cells and downregulates the tumor suppressor Wee-1 (Enders 2010). Wee-1 regulates several cellular processes including mitosis, microtubule stabilization, and phosphorylation of Hsp90 (Hashimoto et al. 2006; Garcia et al. 2009; Mollapour et al. 2010). Although inactivation of Wee-1 by miR-155 represents one of the hallmarks of inflammatory carcinogenesis (Enders 2010; Butz et al. 2010; Tili et al. 2011), its contribution to sarcomagenesis needs to be addressed. These data suggest that miRNAs may be potential molecular classifiers, early detection biomarkers, and therapeutic targets for certain cancers including sarcomas.

Inflammatory mediators in sarcoma

IL-1, IL-6, IL-8, RANKL, TNF, HSPs

Several lines of evidence indicate that inflammation has been implicated in sarcomagenesis leading to the activation of the key transcription factors NF- κ B, STAT-3, and HIF-1 involved in a complex inflammatory network. These factors modulate the expression of a broad panel of tumorigenic factors affecting proliferation, migration, survival, angiogenesis, invasiveness, metastasis as well as radio- and chemoresistance of tumors. Among them, IL-1 acts as crucial player in inflammation-associated carcinogenesis. IL-1 is produced directly by cancer cells or by cells of the microenvironment and stimulates other cell types to produce proangiogenic and prometastatic mediators (Voronov et al. 2007). IL-1 upregulated antiapoptotic Bcl-2 and downregulated proapoptotic Bax in KS cells thus linking escape from apoptosis to immune dysregulation associated with KS (Simonart and Van Vooren 2002). IL-1 and TNF enhanced GM-CSF release from human astrocytes and glioblastoma cells, respectively (Frei et al. 1992; Curran et al. 2011). In human neuroblastoma and glioblastoma cells, GM-CSF exposure mediated cytoprotection by inhibiting saturosporine-induced expression of p53 and Bax, and upregulating Bcl-2 (Huang et al. 2007; Choi et al. 2007). These data imply the crucial involvement of GM-CSF in modulating pro- and antiapoptotic gene expression in inflammation-driven sarcomagenesis. Hönigke et al. (2012) demonstrated a strong IL-6 and IL-8 production by human OS cells after IL-1 stimulation. IL-6 and IL-8 are pleiotropic proinflammatory cytokines that enable tumor growth and inhibit apoptosis in numerous human cancers. In CS cells, IL-1 exposure strongly induced IL-6 production and upregulated secretion of MMP-1 and MMP-13 (Radons et al. 2006b). Experiments with pharmacological inhibitors clearly revealed a contribution of the p38MAPK and/or PI3K/JNK (c-Jun N-terminal kinase) pathway to IL-1-

induced IL-6 secretion in CS cells (Radons et al. 2006a). Elevated serum levels of IL-1, IL-6, and TNF can be found in MFH (Ishii et al. 1991), ovarian FS (Fukuda et al. 2001), and cholesteatoma (Sastry et al. 1999; Akimoto et al. 2000; Yetiser et al. 2002). Both TNF and IL-1 induce activation of NF- κ B, the key orchestrator in tumorigenesis, regulating the expression of several inflammatory mediators promoting tumor growth and invasiveness. Increased serum levels of angioproliferative cytokines, including IL-6, IL-8, macrophage-colony stimulating factor, basic fibroblast growth factor (bFGF), TNF, and VEGF have also been reported in sarcoma patients correlating with poor overall survival (Feldman et al. 2001; Rutkowski et al. 2003). In this context, NF- κ B-dependent MMP-2/-9 expression in STS biopsies correlated with metastasis and grade in LS, while lack of tissue inhibitor of metalloproteinase 2 expression was identified as a poor prognostic factor for disease-free survival in SS (Benassi et al. 2001).

The pleiotropic cytokine TNF plays a dual role in tumorigenesis. On the one hand, TNF is destructive to tumor vasculature and induces necrosis and apoptosis of tumor cells at high concentrations. On the other hand, TNF is a key intermediary of cancer-associated chronic inflammation and has emerged as an important risk factor for tumorigenesis, tumor progression, invasion, and metastasis. TNF not only induces its own secretion but it also upregulates production of other inflammatory mediators thereby stimulating cellular proliferation and differentiation. Stimulation of human OS cells with TNF increased bone sialoprotein (*BSP*), *IL6*, and *PGHS2* mRNA levels (Nakayama et al. 2004). TNF contributes to bone remodeling and represents a component of the receptor activator of NF- κ B (RANK)/RANK ligand (RANK/RANKL) pathway (Silva and Branco 2011). Expression of RANKL could be demonstrated in Paget's sarcoma stromal cells (Sun et al. 2006), OS cells (Mori et al. 2007), bone stromal cells from giant cell tumors (Ng et al. 2010), and ES cells (Taylor et al. 2011). The expression of RANKL increases in response to IL-1 in mesenchymal stromal cells of multiple myeloma patients in a MEK/ERK-dependent manner (Fernandez et al. 2010).

It has been shown previously that several inflammatory mediators and signaling molecules such as NF- κ B and TNF are strictly bound to chaperones/HSPs gene expression and protein functions. In this context, the NF- κ B subunit p65/RelA functions as a transcription factor for numerous HSPs including Hsp60 and Hsp70 (Guzhova et al. 1997; Wang et al. 2010; Cappello et al. 2011) that in turn may have anti-apoptotic functions in cancer cells (Ciocca and Calderwood 2005; Rappa et al. 2012). Several HSPs are implicated with the prognosis of specific cancers, in particular Hsp27, whose expression is associated with poor prognosis. High expression levels of Hsp27 and Hsp60 are reported in OS in which the higher Hsp27 expression correlated significantly with distant metastasis, histological subtype, and poor prognosis (Uozaki

et al. 2000; Moon et al. 2010). Upregulated Hsp60 expression in biopsy specimens together with elevated serum levels of anti-Hsp60 antibodies could be demonstrated in OS patients rendering Hsp60 a putative novel marker in OS diagnosis (Trieb et al. 2000a). Moreover, Hsp70 expression correlated with low tumor differentiation in CS and thus may open the way to novel experimental and diagnostic strategies (Trieb et al. 2000b). A more recent study provided evidence for the oncogenic role of Hsp90B1 and identified miR-223 as the upstream regulator of Hsp90B1 in human OS (Li et al. 2012a). The same study clearly revealed an antitumoral role of miR-223 via the PI3K/AKT/mTOR pathway rendering miR-223 a promising tool in OS therapy.

PGHS-2, VEGF, MMP, emmprin

PGHS-2 has emerged as another NF- κ B-regulated proinflammatory mediator in tumorigenesis. Aberrant or increased expression of PGHS-2 has been shown in a variety of sarcomas including CS, OS, and RMS. PGHS-2 and prostaglandins contribute to carcinogenesis by stimulating cell proliferation, apoptosis, angiogenesis, and metastasis (Kundu and Surh 2012). Overexpression of PGHS-2 leads to secretion of large amounts of VEGF, and therefore is associated with increased tumor cell invasion and poor prognosis (Raut et al. 2004; Ladetto et al. 2005). Although PGHS-2 overexpression has been associated with poor prognosis and decreased survival in CS and OS, no relationship between PGHS-2 expression and patient outcome has been demonstrated in RMS or SS (Carmody Soni et al. 2011) and uterine carcinosarcoma (Menczer et al. 2010).

Among the various proangiogenic factors present in tumors and microenvironment, VEGF has been identified as a crucial player in sarcomagenesis. As demonstrated by our group, human OS cells spontaneously release high amounts of invasiveness- and angiogenesis-promoting MMP-2, VEGF, and IL-8 that can be further enhanced by IL-1 suggesting a crucial contribution to osteosarcomagenesis (Hönicke et al. 2012). VEGF blockade induced cell death in human astrocytoma and FS cells thereby confirming the central role of VEGF in sarcomagenesis (Lee et al. 2011). We also detected a massive release of proangiogenic MMP-1 and MMP-13 in CS cells after IL-1 exposure highlighting the crucial impact of inflammatory mediators in bone sarcomagenesis (Radons et al. 2006b). Similar to IGF, VEGF receptor ligation activates the PI3K/AKT/mTOR and Ras/Raf/MAPK pathways promoting angiogenesis, proliferation, differentiation, and survival. Exposure of CS cells to OPN led to upregulation of MMP-9 through activation of FAK, MEK, ERK, and NF- κ B (Chen et al. 2009). Treatment of these cells with the NF- κ B inhibitor PDTC, the I κ B protease inhibitor TPCK, RGD peptide, anti- α v β 3 integrin monoclonal antibody or MEK inhibitors (PD98059, U0126) inhibited the OPN-induced MMP-9 upregulation providing in vitro evidence for the role of OPN

in angiogenesis and invasiveness of sarcoma. Remarkably, transfection of murine neuroblastoma cells with OPN did not increase VEGF production and did not affect gene expression of other proangiogenic factors suggesting a proangiogenic role independent of VEGF in this sarcoma subtype (Takahashi et al. 2002). Other proangiogenic factors are differentially upregulated in STS cells such as angiopoietin-2, bFGF, Notch-1/-4, and PDGF (Engin et al. 2009; Lee et al. 2010; Ye et al. 2012; Bai et al. 2012; Martin Liberal et al. 2012). Some chromosomal translocations and their gene products are able to upregulate the transcription of proangiogenic *VEGF*, *HIF1A*, *MDK*, *CMET*, and *TIMP2* in ASPS cells (Quesada and Amato 2012). Secretion of inflammatory mediators such as VEGF, IL-1, IL-13, bFGF, G-CSF, and PDGF can be induced in human MM cells exposed to asbestos (Hillegass et al. 2010). In this context, the transcription factor FoxM1 is required for invasion and angiogenesis of glioma cells as VEGF was identified as a direct transcriptional target of FoxM1B (Zhang et al. 2008). While FoxM1 overexpression increased the angiogenic ability of glioma cells, FoxM1 blockage suppressed it. According to Agulnik (2012), the PI3K/AKT/mTOR pathway has an important role in the regulation of angiogenesis mediated by HIF-1 α . Preclinical and clinical studies provide further evidence for the antiangiogenic effects of specific mTOR inhibitors in sarcoma. mTOR has recently been identified to directly phosphorylate HSF-1 (Chou et al. 2012). HSF-1 likewise controls expression of HSPs referred to as the heat shock response (HSR). HSR is highly significant in human pathology, as HSP levels increase in cancer and promote tumorigenesis (Ciocca et al. 2013). Thus, cancers including sarcomas exhibit activated HSF-1 and increased HSP levels that may help to restrain antitumor responses (Zanini et al. 2008). Moreover, the transmembrane glycoprotein emmprin is expressed on tumor cells and induces the production of MMPs in peritumoral fibroblasts thus promoting tumor growth and invasiveness. Epithelioid sarcoma cells have been shown to express emmprin and to upregulate MMP-2 in fibroblasts in coculture experiments critical for epithelioid sarcoma cell stromal invasion and vascularization (Koga et al. 2007). These findings render tumor-associated emmprin a novel and potentially useful target in the therapy of certain STS.

Therapeutic implications

Targeting the molecular pathways involved in sarcomagenesis is the subject of intense basic and clinical research. Antagonistic antibodies, TK inhibitors, and inhibitors of downstream molecules of the PI3K/AKT/mTOR pathway demonstrated encouraging activities. Among them, monoclonal antibodies against IGF-1R such as figitumumab, cixutumumab, and ganitumab, either alone or in combination with other agents, are currently

under investigation for sarcoma patients. Preliminary data of treatment with cixutumumab in patients with advanced or metastatic STS and ES revealed clinical benefit in adipocytic sarcoma patients (Schoffski et al. 2011). Anti-IGF therapy represents a promising therapeutic option in the treatment of sarcoma because it also affects mTOR, one of the downstream effector molecules of PI3K. Therefore, mTOR inhibitors have been consequently tested for their antitumor potential in sarcoma. Sirolimus, temsirolimus, everolimus, and ridaforolimus are analogs of rapamycin (rapalogs), and function as specific mTOR inhibitors (Martin Liberal et al. 2012). Clinical trials analyzing the clinical efficacy of rapalogs in monotherapy or combination therapy in sarcomas are ongoing. A variety of drugs targeting angiogenesis are also being tested in sarcomas. There is now a wealth of evidence indicating that monoclonal antibodies such as bevacizumab and TK inhibitors (axitinib, brivanib, cediranib, imatinib, pazopanib, sorafenib, sunitinib) harbor promising activity and safety in certain subtypes of sarcoma.

Most of the chemopreventive agents tested have been found to suppress NF- κ B and STAT-3 (Yu et al. 2009; Chaturvedi et al. 2011). Moreover, lifestyle-related agents including berberine, curcumin, resveratrol, and piperazine are able to inhibit NF- κ B (Aggarwal and Gehlot 2009). With respect to sarcoma, the selective NF- κ B/PGHS-2 inhibitor celecoxib induced apoptosis and reduced β -catenin protein required for cell survival in human OS cells via downregulation of PI3K/AKT (Xia et al. 2010; Liu et al. 2012; Hönicke et al. 2012). Celecoxib prevented lung metastasis in a murine model of ES without affecting tumor size or neovascularization (Gendy et al. 2011). Clinical trials with celecoxib for sarcoma treatment are infrequent. In a phase II study, the combination of low-dose antiangiogenic vinblastine/celecoxib with standard multiagent chemotherapy for patients with metastatic ES revealed a better 24-month event-free survival for those with isolated pulmonary metastases (Felgenhauer et al. 2013). Interestingly, the antimicrobial fish peptide pardaxin exhibited antitumor activity toward murine FS by downregulating STAT-3 and p65/RelA (Wu et al. 2012). A clinical phase II study with metastatic cancer patients, evaluating the protective effects of the semisynthetic flavonoid 7-mono-O-(β -hydroxyethyl)-rutoside on doxorubicin-induced cardiotoxicity, revealed a 75 % response rate in STS patients (Bruynzeel et al. 2007), most probably via inhibition of NF- κ B (Jacobs et al. 2011). Curcumin from turmeric inhibited growth of LMS and OS cells via inhibition of PI3K/AKT/mTOR and Notch-1, respectively (Wong et al. 2011; Li et al. 2012b) and induced apoptosis and cell cycle arrest in ES cells (Singh et al. 2010). In human OS cells, green tea polyphenols induced apoptosis by decreasing amount and activity of NF- κ B, downregulating Bcl-2 and upregulating Bax (Hafeez et al. 2006). Combinatorial treatment of human OS cells with IL-1 receptor antagonist (anakinraTM) and the green tea catechin (-)-epigallocatechin-3-gallate (EGCG) resulted in a marked

inhibition of IL-1-induced tumorigenic factors (Hönicke et al. 2012). However, clinical trials with antioxidants such as EGCG and curcumin are lacking up to date.

Novel approaches in limiting sarcoma growth include thalidomide (McMeekin et al. 2012), monoclonal antibodies directed against c-Kit (Edris et al. 2013), Cdk inhibitors such as roscovitine (seliciclib; Lambert et al. 2008), flavopiridol (Luke et al. 2012), and dinaciclib (Fu et al. 2011), as well as the epidermal growth factor receptor inhibitor erlotinib (Abraham et al. 2011; Xie et al. 2011), the c-Met inhibitor tivantinib (ARQ197; Wagner et al. 2012), and the Hsp90 inhibitor retaspimycin hydrochloride (IPI-504; Dickson et al. 2013).

Concluding remarks

Sarcomas represent a heterogeneous group of mesenchymal malignancies that very often lead to death. Their management requires a multidisciplinary team approach. Despite their low incidence in comparison to other tumors, the development of effective therapeutical approaches is essential. In the past years, an increasing number of new targets have been identified in the treatment of sarcomas leading to the development of new drugs that need to be tested. Novel targets include histone deacetylase and anaplastic lymphoma kinase (ALK). The latter has been found as being upregulated in approximately half of inflammatory myofibroblastic tumors (IMT). A phase I trial reported a sustained partial response to the ALK inhibitor crizotinib (PF-02341066) in a patient with ALK-translocated IMT suggesting a therapeutic strategy for genomically identified patients with this aggressive STS (Butrynski et al. 2010). Inflammatory pathways including sonic Hh and Notch are further critical targets in both, prevention and therapy of sarcomas. Clinical trials of the Hh inhibitor GDC-0449 and the Notch inhibitor RO4929097 as well as the histone deacetylase inhibitor vorinostat are ongoing with no results up to date. Since tumorigenesis is caused by dysregulation of multiple pathways and crosstalk between them, the best therapeutic outcome might be achieved by combining agents with distinct modes of action. Nutraceuticals are a reasonable choice due to their safety and ability to suppress multiple targets including NF- κ B, STAT-3, and Notch. Targeting NF- κ B should also reduce the expression of pro-tumoral HSPs and could thus be considered a form of therapeutic use of chaperones termed “chaperonotherapy”. All the data mentioned before clearly demonstrate that there is a strong medical need for the development of new concepts how such inflammatory activities working in sarcomagenesis may be therapeutically targeted with novel combinations of chemopreventive drugs. Our own findings favor a therapeutic approach which combines the IL-1/NF- κ B activity suppressing effects of IL-1 receptor antagonist and the anti-angiogenic and anti-inflammatory activities of certain phytochemicals such as

EGCG because it might impair the development of the malignant phenotype in sarcoma and produce a crucial additive or synergistic antitumoral response compared to single-agent therapies. The strategy of inhibiting multiple pathways simultaneously in sarcoma is currently under investigation. An intriguing novel approach in sarcoma treatment relates to oncolytic virotherapy. Preclinical data revealed that oncolytic viruses exhibit potent oncolytic effects against human sarcomas (Li et al. 2011; He et al. 2012). As our knowledge of the molecular pathways involved in sarcomagenesis is improving, targeted therapies aiming to interrupt the vicious connection between inflammation and sarcoma are about to come.

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