

Undervalued ubiquitous proteins

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Received 5 March 2018, Accepted 21 January 2019

Abstract - The role of ubiquitous proteins (UPs) and their corresponding enzymes have been underestimated in carcinogenesis as the focus of much research revolved around measuring mutations and/or other genetic epiphenomena as surrogate markers of cancer and cancer progression. Over the past three decades, the scientific community has come to realize that the concentration on microdissection of cancer cells without accounting for the neighborhood in which these cells reside, i.e., the stroma, fails to reflect the true nature of cancer biology. UPs are fundamental for cellular homeostasis and phylogenetic development as well as for the integrity of the cytoskeleton and for the stability of cells and tissues in regards to intercellular signaling, cell shape and mobility, apoptosis, wound healing, and cell polarity. Corresponding enzymes are used by microorganisms to gain entry into the host by degradation of UPs and play a role to cleave peptide bonds for killing disease-causing life forms along for the creation of the precancerous niche (PCN) during carcinogenesis, cancer invasion, and in metastasis. The language used by such proteins as well as their complementary enzymes with its influence on multiple pathways and the cross-linked extracellular matrix is incompletely understood. The role of UPs in the disruption of signaling homeostasis and resulting interference with crosstalk in carcinogenesis appears sufficiently delineated to warrant a much more refined examination of their qualitative and quantitative contribution to the development of cancer and cancer therapy.

Keywords: Autophagy, cancer, carcinogenesis, cell transition, chronic inflammation, collagen, collagenase, crosslinking, cytoplasm, cytoskeleton, decorin, degradation, desmosin, ECM, elastin, elastase, epidermis, epigenetics, epithelium, extracellular matrix, fibroblast, fibromodulin, fibronectin, fibrosis, genomics, inflammation, keratin, keratinase, lysyl oxidase, metaplasia, microRNA, mutation, pathogenesis, polypeptides, precancerous niche, proteins, proteoglycan, proteomics, signaling, vimentin

Introduction

The role of ubiquitous proteins (UPs) and their corresponding enzymes have been underestimated in carcinogenesis as the focus of much existing research revolves around measuring mutations and/or other genetic epiphenomena as surrogate markers of cancer and cancer progression. Over the past three decades, the scientific community has come to realize that the concentration on microdissection of cancer cells without accounting for the neighborhood of cancer cells (i.e., the stroma) fails to reflect the true nature of cancer biology.

Ubiquitous proteins (UPs)

Proteins are macromolecules consisting of amino acids connected by peptide bonds. The building blocks of

proteins and polypeptides contain an acid amino group (CHOO), a basic amine group (NH₂), a hydrogen atom, a variable side chain, and a central C-atom [1]. Side chains can be nonpolar (e.g., glycine, alanine, valine, leucine, and isoleucine), charged polar (e.g., glutamic acid, aspartic acid, histidine, lysine, and arginine), non-charged polar (e.g., cysteine, methionine, threonine, serine, proline, glutamine, and asparagine), and aromatic (e.g., phenylalanine, tryptophan, and tyrosine). The primary structure describes the sequence of the individual amino acids in polypeptide chains. With this linear 2D primary structure, 3D structural elements develop which are arranged to form the spatial structure of a protein. Additionally, single proteins can assemble to form one functional protein or a protein complex, called a quaternary structure.

For the study of proteins in general, one needs to be careful as false negative or false positive results can occur. Using formalin and paraffin fixation can result for keratin and vimentin assays yields false negative findings [2] which

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may skew the interpretation of data when using immunohistochemical studies to investigate cytoskeletal proteins and their role in carcinogenesis. Alcohol-fixed specimens showed 100% staining against vimentin while this decreased to 63% in formalin-fixed tissues [3], a finding that was subsequently reproduced [4].

The concentration on microdissection of cancer cells without accounting for the stroma fails to reflect the true nature of cancer biology [5]. Several approaches were made to differentiate between different stroma-associated tumors [6].

The extracellular matrix (ECM) is much more than just a cell-free space between cells. It is not by accident that Robert Hynes stated that the ECM does not consist out of “...just pretty fibrils” [7]. The ECM is a dynamic repository for growth factors [8] and continuously undergoes deposition, degradation, and modification [9]. The complex network of proteins and filaments of the ECM co-regulate cell proliferation, survival, and migration [10]. Various growth factors bind to ECM proteins and additionally a binding of a growth factor to its receptor, such as fibroblast growth factor (FGF) to fibroblast growth factor receptor (FGFR) needs simultaneous chain-binding to heparin sulfate which functions as a cofactor ([11] reviewed in [7]). To measure various proteins and filaments is a challenge as proteins are often “*large, cross-linked and covalently bound, heavily glycosylated*” ([12,13] reviewed in [14]).

UPs include keratin, keratinase, collagen, collagenase, elastin, elastase, vimentin, fibronectin, and decorin. The language used by such proteins influences multiple pathways and affects the ECM in ways that are still incompletely understood. A closer look at each of these UPs illustrates what is presently known of their role in cancer.

Keratin

Detailed information about the chemistry of keratins (KRTs) was published in 1965 [15]. The mechanical properties were reported in 1980 [16] and extensively reviewed [17]. Keratin occurs in vertebrates, birds and reptiles. It is the major component of skin, hair, nails, teeth as well in hooves and horns. Keratin is considered to be nonreactive and mechanically durable. The largest gene family in KRTs was shown to contain up to 54 functional genes [18] which are clustered on chromosomes 12q13.13 and 17q21.2 with differing expression patterns ([19] reviewed in [20]). The importance of KRTs goes beyond maintaining the integrity of the cytoskeleton and its role in the stability of cells and tissues to intercellular signaling, apoptosis, wound healing, and cell polarity [18]. Although the impact of KRTs in carcinogenesis has not been elucidated, it has been suggested that mitosis can be both regulated and promoted by KRTs [21].

The characteristic of KRTs as being inflexible and hard is based on the cysteine disulfide bridges which create a helical shape and sulfide atoms which bond to each other such that the resulting fibrous matrix is not readily

soluble. The number of cysteine bridges contributes to the strength of the bonds in keratin. Sequences of keratin were first reported in 1982 when two different types were identified: Type I and II keratin [22]. Crystal structure analysis confirmed α - and β -helical conformations [23]. Different KRTs were identified, and in 2006 a consensus nomenclature for mammalian KRTs was proposed and accepted [24]. Twenty cyto-keratins were identified with molecular masses between 40 and 68 kDa, abbreviated as KRTs. KRT 1-8 contain eight neutral-basic KRTs while KRT9-20 contain 12 acid keratins. KRTs are dimers composed of neutral-basic and acid KRTs subunits and many dimers come together to form protofilaments, followed by further dimerizing to form protofibrils; protofibrils form tetramers called microfibrils and microfibrils associate into macrofibrils [18]. The distribution pattern of these complexes differs in different epithelial cells, and antibodies against the subtypes KRT1-20 have been developed for use in pathology with the goal to determine the origin of tumor metastases.

The epidermis contains multi-layered keratinizing epithelium (KRT1-9 and KRT2-10), the epithelium of the mouth, pharynx, larynx, esophagus, anal canal, vagina, uretra contain multi-layered non-keratinized squamous epithelium (KRT4-13) or (KRT6A with KRT16 or KRT17) while the epithelium of the respiratory tract consists of basal cells of complex epithelial cells (KRT5 with KRT14 or KRT15). Epithelia of all mucosal cells in the stomach and bowel are layered epithelium and luminal glandular cells (KRT7-19 or KRT8 with KRT18 or KRT20). This pattern of distribution shows that keratin is a widespread protein in nature and is also found in the nuclei and cytoplasm of almost all differentiated eukaryote cells [25].

Hepatocyte activator inhibitor type 1 (HAI-1) has been shown to be critical in maintaining normal keratinocyte morphology [26] and KRT19 has been shown to be a putative cancer stem cell (CSC) marker associated with epithelial-mesenchymal transition (EMT) and transforming growth factor beta (TGF- β)/Smad signaling [27]. KRT8 was observed to be expressed to a lesser degree in primary tumors while it was positive in lymph node metastasis [28] which implies that the earliest degradation starts within the PCN in primary tumors and not in locations where cancer subsequently spreads.

It was reported some 50 years ago in a study of 115 autopsies and 168 surgically excised specimens of patients with irradiated squamous cell carcinomas of various sites that despite necrosis, extensive and marked keratogenesis were characterized by abundant central masses of hyperkeratotic tissues [29]. Therefore, hyperkeratinization is likely to be an early step as a reaction to keratinase before degradation of the tissue. Radiation-induced keratogenesis was suggested to represent a survival strategy of damaged cancer cells as hyperkeratosis with squamous metaplasia was also observed in chronic inflammation. Periodic biopsies during irradiation of 28 patients with squamous cell carcinoma of the mouth and oropharynx showed that small daily doses of radiation

resulted in hyperkeratotic tissue of radio-resistant cells next to pockets of destroyed cancer cells [30].

KRTs found in the cytoplasm, cytoskeleton, and epithelial cells are named cytokeratins and are components of intermediate filaments. It is known that cytokeratins are of importance for phylogenetic development as well for the identification of the origin of cells for diagnosing cancerous lesions [31] such as an estimation of apoptosis/necrosis ratio in liver diseases. However, KRTs have a greater tendency for cross-linking and Mallory bodies in chronic liver disorders underlie a chemical memory in terms of the causative factor, alcohol. This phenomenon was shown to be reversible. Furthermore, the degeneration of hepatocytes and the promotion of fibrosis is correlated with the expression of cytokeratin 18 and its caspase-cleaved fragments [32].

Keratinase

Keratinase, an enzyme that breaks down keratin, is obtained from fungi, bacteria, and actinomycetes for industrial purposes for the preparation of animal nutrients, protein supplements, leather manufacture, textile processing, detergent formulation, feather meal processing for feed and fertilizer, the pharmaceutical and biomedical industries, and waste management (reviewed in [33,34]), yet no highly sensitive assay is available to detect keratinase.

The hydrolysis of strongly cross-linked keratin can be done by microbial proteolytic keratinases [35]. Since then, many microorganisms such as bacteria as well as dermatophilic fungi have been shown to degrade keratin by keratinolysis [36,37]. Dermatophytes, such as *Tryptophan rubrum*, secrete keratinases and other enzymes that allow the dermatophyte to burrow deeper into the stratum corneum, and the polysaccharide, Mannan, with a lipophilic toxin can inhibit cell-mediated immunity [38]. It was suggested that membrane potential plays a role in keratin degradation to make the chains available for cleavage by proteinases [39].

The keratinocyte growth factor (KGF), identified in 1989, and shown to exert its effect in a paracrine manner, is limited to epithelial cells [40] and is likely responsible for the remarkable aggressiveness and proliferation of scirrhous gastric cancer cells in a paracrine manner [41]. KGF is released by fibroblasts in wound healing, participates in epidermal homeostasis in regard to epithelial proliferation, differentiation, and migration, and binds to fibroblast growth factor receptor 2 (FGFR2b) [42–44]. The E5 oncoprotein of human papillomavirus type 16 (HPV16 E5) decreases KGFR/FGFR2b [45] resulting in the deregulation of signal transduction [46], and the induction of interferon regulatory factor 1 (IRF-1) stimulating interferin beta (IFN- β) [47]. One regulation of KGFR is by the transcription factor E2F1: knockout of activated aryl hydrocarbon receptor (AhR) led to KGFR downregulation and transfection with siRNA specific for AhR (siAhR) reduced E2F1 in the nucleus [48]. Thereby

AhR-E2F1-KGFR signaling is actively involved in epithelial cell proliferation and early carcinogenesis. However, papilloma viruses are not just important for the development of human cancer but also a problem in veterinary medicine including for canines, felines and bovine species [49].

Collagen

Collagen is present in all multicellular organisms and is the most abundant protein in vertebrates [50–52]. Extracellular proteins form insoluble fibers with great tensile strength. Collagen is a major stress-bearing component of connective tissue found in bone, teeth, cartilage, tendon, skin, etc. and mammals have at least 33 distinct collagen subunits that form >20 different quaternary structures. Nearly 33% of the residues in collagen have glycine (Gly) as the primary amino acid, and another 15–30% have Pro (4-hydroxyproline) with a smaller fraction containing 3-hydroxyproline and 5-hydroxylysine. The enzyme converting Pro to 4-hydroxyproline is prolyl hydroxylase which requires ascorbic acid (vitamin C) to be activated.

Repeating Gly-X-Y sequences comprise collagen's quaternary structure with Pro typically found in the X-position and hydroxyproline in the Y-position. These three collagen polypeptides are wrapped around each other forming a right-handed triple helix. In every third position, Gly is required for achieving the close-packing of the subunits. By comparison to keratin's crosslinking with disulfide bonds, cross-links in collagen are between Lys (and His) residues because collagen is nearly devoid of Cys.

Lysyl oxidase (LOX), a copper-dependent enzyme, is known to form crosslinks of the ECM by oxidative deamination converting a specific lysine and hydroxylysine residue in collagen to peptide-bound aldehydes which can be irreversibly inhibited by β -amino-propionitrile (β APN), a copper chelator [53]. The ability of an agent or enzyme to inhibit crosslinks depends on the types of crosslinks that stabilize that particular collagen fiber.

Collagenase

The role of collagenase, produced by inflammatory cells, and required to degrade collagen has been known for some 40 years and denaturation can result in gelatin formation [54]. Metalloproteinases (MMPs) are associated with breast cancer development and “*can be loosely divided into four main groups: the interstitial collagenases, gelatinases, stromelysins, and membrane-type MMPs*” [55]. MMP-mediated degradation of type I collagen (C1M), type IV collagen (C4M), and citrullinated vimentin (VICM) appear important for remodeling-mediated matrix and have been investigated in 5855 Danish samples in The Prospective Epidemiologic Risk Factor (PERF I) study: C1M and VICM were associated with survival in postmenopausal cancer and C1M was identified as an independent risk factor for cancer-specific mortality [56].

The expression of type IV collagenase is modulated by influenza A/Beijing/353/89 (H3N2) virus at the transcriptional level, is dependent on the epithelial cell line under investigation through matrix MMP-9 (in Vero cells), and on matrix MMP-2 in Madin-Darby canine kidney (MDCK) cells [57]. Interestingly, investigation of matrix MMP-13 in serum and saliva and collagenase-3 in a pre-malignant condition (oral lichen planus) and in cancer (oral squamous cell carcinoma) revealed nearly equal levels, although serum MMP-13 was associated with unstimulated and not stimulated saliva MMP-13 [58].

The enzymes of named UPs seem to play a role in the dissemination of cancer. For example, in breast cancer a switch of the kinase-MMP network was observed: neuregulin (NRG) augmented MMPs expression by extracellular signal-regulated kinase 1 (Erk1, mitogen-activated protein kinase 3, MAPK3)/extracellular signal-regulated kinase 2 (Erk2, mitogen-activated protein kinase 1, MAPK1) and increases collagenase 3 expression by controlling the activity of a myotubularin-related protein 5 (SBF1) related transcription factor [59].

Elastin

Augmented or condensed elastin in breast cancer was first described in 1957 [60] and alterations in collagen and elastin along epithelial and stromal junctions in breast cancer were reported in 1970 [61]. Although Lundmark showed some 70% elastosis in breast cancer tissue, the real elastin content could not be determined as differences in irradiated and non-irradiated tissue were found along with a shift to higher incidences in patients over 40 yr [62]. Elastin is a fibrous protein in vertebrates and is responsible for shape as it lends compliance to large blood vessels and organs such as lungs, liver, spleen, and skin [63]. Elastin has a composition similar to collagen. It however does not contain hydroxylysine, but instead contains a significant proportion of valine (15.6%). Lysine residues can be oxidized by LOX to allysin and each three allysin plus a lysine may be converted into an annular desmosin contributing to the resilience of the whole molecule. The soluble precursor is tropoelastin. Hereditary diseases such as *Williams-Beuren syndrome* or congenital subvalvular aortic stenosis (SVAS) can be caused by mutations within the elastin gene.

The protein network in elastin consists of cross-linked elastin units and the cross-linking enzyme, LOX, remodels elastin after it has been secreted from cells in soluble form. The amino acid, Lys, is responsible for this cross-linking. Proteases, such as elastase, are important in humans as they cleave peptide bonds and neutrophil granulocytes release specific elastase granules for killing microorganisms.

Elastase

Elastase in bacteria was isolated and described in 1960 [64,65] and in fungi in 1967 [66] and many fungi have since been shown to have elastases [67]. Later it was found that proteases, such as elastase, are widely distributed in the

human, bacterial, and fungal world [68,69]. Elastase was shown to promote fibroblast differentiation in lung fibrosis [70] and inhibiting elastase was shown in the bleomycin-fibrosis model to prevent fibrosis [71]. Elastases in mammals are found mainly in pancreas and neutrophil granulocytes, and in macrophages while non-mammalian species show great variability of bacterial metallo- and serine- elastases [72] and the elastases are understood to be a virulence factor in bacteria such as *Pseudomonas aeruginosa*. Bacterial elastase was shown to cleave tight junctions as well as cleave IgA, IgG, C3bi, and CR1 contributing to decreased immune responses in the host [73]. Elastases belong to the class of serine proteinases, cysteine proteinases, and MMPs, and play seemingly important roles in both inflammation and fibrosis [72]. Elastase activity was demonstrated to be of importance for cancer invasion in human bladder cell lines in vitro; secreted elastase was shown only in 8% of samples revealing that elastase was primarily involved at the cell surface and not secreted by those cells [74].

Pancreatic elastase (PE) and neutrophil elastase (NE) were both isolated in pancreatic carcinoma cells and it was shown that these acinar enzymes are secreted in some 90% of patients with ductal adenocarcinoma [75]. Moreover, four of five pancreatic carcinoma cell lines expressed splicing variants of these enzymes.

Also, viruses code for proteinases but these differ significantly from cellular enzymes as the serine component is replaced by a cysteine residue [76]. Although many pathogenic mechanisms of viruses have not been elucidated, it is thought that proteases secreted in major target organs are of importance. One potential pathway for entry of the virus into the host might be due to proteases such as elastase [77,78]. This reveals that some pathogens enter the cell through their own proteases while others initiate protease secretion within the host.

It was shown in 1969 that cutaneous cells of glandular potential can be converted by the oncogenic virus, SV40, in vivo to adenocarcinomas. The authors showed that this is a rare event as only 4 out of 34 SV40 transformed embryonic skin and subcutaneous tissue cell lines developed an adenocarcinoma while the remaining 30 showed a variety of sarcomas [79]. Therefore, it seems not to be essential for a mesenchymal-epithelial or epithelial-mesenchymal transition to occur but instead it appears critical that a cancer cell develops. Namiki et al. showed in 2009 that continuous exposure and infection with the bacterium mycoplasma, *M. genitalium* or *M. hyorhinis*, can lead into malignant transformation of benign human epithelial cells and served as an appropriate model to distinguish between prostatitis and prostatic carcinomas [80].

Vimentin

The intermediate filament, vimentin, maintains cellular architecture as well as tissue integrity and serves as a marker for cell transition [81,82] as reported in sarcoma [83], in breast cancer [84–86] and in “various epithelial

cancers including prostate cancer, gastrointestinal tumors, CNS tumors, breast cancer, malignant melanoma, lung cancer, and other types of cancers” (reviewed in [87]). It was suggested to be wary of using vimentin for cell transition as it is expressed in various cells, including fibroblasts, endothelial cells, cells of the hematopoietic lineages, and glial cells and because “*adult epithelial cells transiently express vimentin in response to various insults*” ([88] reviewed in [85]). As mentioned above, vimentin is also important for cell transition [89]. Furthermore, vimentin is correlated with mesenchymal cell shape and mobility which is associated with loss of desmosomal contacts [90] and which underpins why the assembly state of vimentin is sensitive altering stiffness and morphology [91]. Matrix stiffness triggers matrix MMPs activity, and matrix stiffness can, independently of matrix density, modify vascular growth and integrity [92].

A small GTPase of the Rab family, Rab7a, regulates cell migration through Ras-related C3 botulinum toxin substrate 1 (Rac1) and vimentin [93]. Here, there is an interconnection with Rac1: Lamellipodin is an actin regulator [94] and depletion decreases pulmonary metastasis in an orthotopic mouse breast cancer model and otherwise “*Lamellipodin promotes invasive 3D cancer cell migration via both actin-elongating Ena/VASP proteins and the Scar/WAVE complex*” [95]. The Scar/WAVE complex is a co-factor and effector in cell migration [96,97]. Guanosine triphosphatase Rac-dependent ECM-stiffening involves focal adhesion kinase (FAK), the adaptor protein p130Cas (Cas), and lamellipodin by which mechanotransduction converts external information by the “*ECM stiffness into stable intracellular stiffness and mechanosensitive cell cycling*” showing that lamellipodin controls cell migration and directly influences and regulates the cell cycle [98]. There is hope that atomic force microscopy (AFM) can better characterizes ECM stiffness in the future [99].

Autophagy is inhibited by a protein kinase B (Akt-, PKB-)-dependent mechanism as vimentin forms a complex with 14-3-3 and beclin 1 and is a canonical marker of cell transition [81]. Higher expression levels of vimentin and positive N-Cadherin have been associated with poor survival and lower disease-free survival in patients with squamous cell carcinoma of the tongue which was significant even when using multivariate Cox regression with adjustments for cell differentiation, pathological stage, and expression levels of Snail, Twist, E-cadherin, and N-cadherin [100]. Vimentin was proposed to be essential in promoting metastatic potential in cholangiocellular carcinoma (CCC) [82]. Vimentin leads to a change of DNA architecture with chromatin disruption in human immunodeficiency virus type I (HIV-1) [101]. Vimentin is also upregulated in gastric cancer together with N-cadherin and slug with down-regulation of E-cadherin by the circular RNA circ-104916 [102]. The fact that vimentin is routinely used for immunohistochemistry in mesenchymal tumors might be relevant and suggests that vimentin release plays a role in mesenchymal tumors.

Fibronectin and decorin

Fibronectins are large glycoproteins released by fibroblasts, macrophages, endothelial cells, chondrocytes, myoblasts, hepatocytes, and amniotic cells with small amounts also being released by intestinal epithelial cells (reviewed in [103]). Cellular fibronectin is typical as a fibrillar ECM although it can also be measured and found as soluble plasma fibronectin. Increased fibronectin levels had been found in benign hyperplasia and in various types of mammary tumors ([104,105] reviewed in [106]) which result in the proliferation and creation of an environment that facilitates cell growth. Increased rigidity occurs during the development of carcinogenesis and the ECM becomes stiff with altered signaling due to its stiffness ([107] reviewed in [106]).

An increase of fibronectin results in the reversal of cell growth arrest including failure to maintain the acinar structure. This is concordant with findings of increased fibronectin in breast cancers [104,105]. More rigid breast tissue is prone to develop hyperplasia and dysplasia including a direct association of density found in mammography and deposition of the proteoglycans, decorin and lumican, together with the presence of hyperplasia ([108,109] reviewed in [106]). It has been shown that increased fibronectin levels stimulate epithelial cells to produce their own fibronectin (reviewed in [106]).

Recently plenty of 113 ECM proteins measured by quantitative proteomics resulted into “*ECM protein signatures unique to fibrosis, primary tumors, or metastases*” [110]. These included several S100 proteins, including fibronectin and Tenascin-C (Tnc) in lung cancers and that tumor progression is induced by the transcription factor Nkx2-1 with subsequent Tnc repression. CRISPR-mediated Tnc activation resulted into metastatic dissemination. Within the cascade of pancreatic islets progression from being hyperplastic to angiogenic to insulinomas, 35 proteins of the ECM were detected in various abundance and “*among these, the core ECM proteins, EFEMP1, fibrillin 1, and periostin were found in higher abundance, and decorin, Dmbt1, hemicentin, and Vwa5 in lower abundance*” [111].

Despite various proteins, such as integrins, even fibronectins help various cancer-triggering pathogenic stimuli to bind such as has been shown for various herpes viruses [112–115], hepatitis viruses [116–118], schistosomiasis [119–123], or opisthorchis [124,125], helicobacter [126–129], or mycoplasma [130–134]. Otherwise autocrine fibronectin inhibits cancer spread [135] and decreased fibronectin seems to be essential during metastasis [136] as natural killer cells (NK cells) mediated control can inhibit metastasis by increase of fibronectin [137].

Recently, the influence of mycoplasma and the bacterial chaperon, DnaK, in carcinogenesis was shown to be dependent on p53 dysregulation [138]. The bacterial molecular chaperone DnaK family (70 kilodalton heat shock protein, Hsp70s) are UPs that are inactivated in an ATP-bound state and become

activated by cellular stress to protect against aggregation. The DnaKs have been reported to be overexpressed in various cancers [139–142], their expression is reduced in esophageal cancers [143], and increased in virus replication [144]. However, the interaction of DnaK and cancer is not just dependent on p53 dysregulation which reveals that focusing on signaling pathways in carcinogenesis is not enough. Mycoplasma infection induces MMP-1 and MMP-9 [145], 5-lipoxygenase (5-LOX, ALOX5, 15-LO-1, 15-LOX-1) and cyclooxygenase 2 (Cox-2) [146], cytochrome P450, family 1, subfamily A, polypeptide 1 (CYP1A1) and interleukin 6 (IL-6) [147], plasmin [148], fibroblasts [149], p107 [150], IL-6, interleukin 1 beta (IL-1b), TGF- β and fibrosis [151], epidermal growth factor receptor (EGFR), phosphatidylinositol 3-kinase (PI3K), Akt, tumor suppressor phosphatase and tensin homolog (PTEN) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) [152–154], deacetylates forkhead box protein O3a (FOXO3a) [155], and downregulates E-cadherin [156].

Furthermore, DnaK is upregulated in keloid tissues and scars [157] which can be basis for tumor development in various cancers [158–160]. In this regard, it may of importance to keep in mind the poor survival of subtypes of colorectal cancers with desmoplastic patterns [161] and the increase of desmoplasia in keloid tissues [162].

Decorin is a small (90–140 kDa in molecular weight) cellular and matrix glycosylated protein (proteoglycan) consisting of a chondroitin sulfate (CS) or dermatan sulfate (DS) encoded by the decorin gene and a component of the ECM [163,164]. The interaction of decorin with fibronectin inhibits fibroblast cell adhesion [165]. Decorin and fibromodulin are overexpressed in breast cancer cell lines associated with downregulation of activation of NF- κ B and TGF- β 1 but fibromodulin has a more effective effect than decorin [166]. Decorin binds to TGF- β stimulating Chinese hamster ovary (CHO) cell proliferation [167,168]. Decorin increases the phosphorylation level of TGF- β receptor 1 (TGF- β R1) resulting in higher levels of TGF- β receptor 2 (TGF- β R2) as well as the expression of p15 with negative feedback on cell proliferation [169,170]. Ongoing TGF- β 1 signaling triggers an 8- to 10-fold increase of decorin some 48 h after TGF- β exposure ceases and decorin binds fibronectin and collagen [171]. TGF- β causes matrix accumulation through proteoglycan synthesis and deposition. Decorin is considered as a “*guardian from the matrix*” by modulation [172].

The proteoglycan, decorin, has regulatory effects on inflammation and cancer growth through the tumor suppressor programmed cell death 4 protein (PDCD4) and miR21 and acts “*as an endogenous ligand of Toll-like receptors 2 and 4 and stimulates production of proinflammatory molecules, including PDCD4, in macrophages*” [173] but otherwise decorin can increase TGF- β activity [174]. Therefore, it seems that the general principle of homeostasis in biology also applies to decorin. Using an adenovirus gene transfer in the breast cancer cell

line, 4T1, revealed a fibromodulin and decorin overexpression with downregulation of NF- κ B and TGF- β 1 [166]. Decorin does not interact synergistically with TGF- β 2 in the presence of fibronectin promoting cell migration, while in the presence of collagen TGF- β 2 fails to inhibit migration. This suggests that decorin can alter the activity of TGF- β 2 [175]. The disruption of decorin homeostasis supported by the finding that cancer progression and poor prognosis in esophageal squamous cell carcinoma (ESCC) is associated with increased decorin levels [176]. Continuous TGF- β overexpression may also leverage the negative feedback decorin mechanism with increases in cell proliferation.

Summary

UPs, once relegated to maintaining cellular structure and morphology, have in recent decades come to be recognized as components that effect the cross-linked ECM and the tumor environment. The language used by such proteins and their complementary enzymes with their influence on multiple pathways and the ECM is incompletely understood. Recent research has shown that UPs and their corresponding enzymes are actively involved early in carcinogenesis with consequent chronic inflammation, fibrosis, formation of the precancerous niche (PCN), chronic matrix stress escape attempts and, when these fail, transition of a normal cell to a cancer cell (NCCCT) occurs. Furthermore, UPs and their enzymes are involved in maintaining the cytoskeletal integrity, cell stability, information exchange by intercellular signaling, inhibition of autophagy and apoptosis. The degradation of UPs appears to be especially important for creating an environment that promotes the dissemination of cancer after a cancer cell has developed. The modulation of the microcosms with consequent dysregulated fine-tuning and induced crosstalk is influenced by UPs and their corresponding enzymes. These data warrant a much more refined examination of the qualitative and quantitative contribution of UPs and their enzymes during the “*Disruption of signaling homeostasis induced crosstalk in the carcinogenesis paradigm Epistemology of the origin of cancer*”.

Nomenclature

| | |
|-------------|---|
| 5-LOX | 5-Lipoxygenase (ALOX5, 15-LO-1, 15-LOX-1) |
| β APN | β -Amino-proprio-nitrile |
| AFM | Atomic force microscopy |
| AhR | Aryl hydrocarbon receptor |
| Akt | Protein kinase B (PKB) |
| C1M | Type I collagen |
| C4M | Type IV collagen |
| Cas | p130Cas |
| CCC | Cholangiocellular carcinoma |
| CHO | Chinese hamster ovary |
| CHOO | Acid amino group |
| Cox-2 | Cyclooxygenase 2 |
| CS | Chondroitin sulfate |

| | | | |
|----------------|--|-----------------|--|
| CSC | Cancer stem cell | Rab7a | Small GTPase of the Rab family |
| CYP1A1 | Cytochrome P450, family 1, subfamily A, polypeptide 1 | Rac1 | Ras-related C3 botulinum toxin substrate 1 |
| DNA | Deoxyribonucleic acid | SBF1 | Myotubularin-related protein 5 |
| DnaK | 70 kilodalton heat shock protein, Hsp70s | siAhR | siRNA specific for AhR |
| DS | Dermatan sulfate | Smad | Intracellular protein transducing extracellular signals from TGF- β ligands into the nucleus |
| E2F1 | E2F transcription factor 1 | SVAS | Subvalvular aortic stenosis |
| ECM | Extracellular matrix | TGF- β 1 | Transforming growth factor beta 1 |
| EGFR | Epidermal growth factor receptor | TGF- β R1 | TGF- β receptor 1 |
| Erk1 | Extracellular signal-regulated kinase 1, mitogen-activated protein kinase 3, MAPK3 | TGF- β R2 | TGF- β receptor 2 |
| Erk2 | Extracellular signal-regulated kinase 2, mitogen-activated protein kinase 1, MAPK1 | Tnc | Tenascin-C |
| ESCC | Esophageal squamous cell carcinoma | UPs | Ubiquitous proteins |
| ETM | Epithelial-mesenchymal transition | VICM | Citrullinated vimentin |
| FAK | Focal adhesion kinase | | |
| FGF | Fibroblast growth factor | | |
| FGFR | Fibroblast growth factor receptor | | |
| FGFR2b | Fibroblast growth factor receptor 2 | | |
| FOXO3a | Forkhead box protein O3a | | |
| Gly | Glycine | | |
| H3N2 | Influenza A/Beijing/353/89 virus | | |
| HAI-1 | Hepatocyte activator inhibitor type 1 | | |
| HIV-1 | Human immunodeficiency virus Type I | | |
| HPV16 E5 | E5 oncoprotein of human papillomavirus type 16 | | |
| Hsp70s | 70 kilodalton heat shock protein, DnaK | | |
| IFN- β | Interferon beta | | |
| IL1- β | Interleukin 1 beta | | |
| IL-6 | Interleukin 6 | | |
| IRF-1 | Interferon regulatory factor 1 | | |
| KGF | Keratinocyte growth factor | | |
| KRTs | Keratins | | |
| LOX | Lysyl oxidase | | |
| MAPK1 | Mitogen-activated protein kinase 1, extracellular signal-regulated kinase 2, Erk2 | | |
| MAPK3 | Mitogen-activated protein kinase 3, extracellular signal-regulated kinase 1, Erk1 | | |
| MDCK | Madin-Darby canine kidney | | |
| MMPs | Metalloproteinases | | |
| MMP-1 | Metalloproteinase-1 | | |
| MMP-2 | Metalloproteinase-2 | | |
| MMP-9 | Metalloproteinase-9 | | |
| MMP-13 | Metalloproteinase-13 | | |
| NCCCT | Normal cell to a cancer cell transition | | |
| NE | Neutrophil elastase | | |
| NF- κ B | Nuclear factor kappa-light-chain-enhancer of activated B cells | | |
| NH2 | Basic amino group | | |
| NK cells | Natural killer cells | | |
| NRG | Neuregulin | | |
| PCN | Precancerous niche | | |
| PDCD4 | Programmed cell death 4 | | |
| PE | Pancreatic elastase | | |
| PERF I | Prospective epidemiologic risk factor I study | | |
| PI3K | Phosphatidylinositide 3-kinase | | |
| PKB | Protein kinase B (Akt) | | |
| Pro | 4-Hydroxyproline | | |
| PTEN | Phosphatase and tensin homolog | | |

Acknowledgement

The manuscripts of this Special Issue were supported by the Theodor-Billroth-Academy[®] (TBA[®]) and INCORE, (International Consortium of Research Excellence) of the (TBA[®]). We express our gratitude to the discussions on the web group of the Theodor-Billroth-Academy[®] (TBA[®]) on LinkedIn, the exchange with scientists at Researchgate.com, as well as personal exchanges with distinguished colleagues who stimulated our thinking all named individually earlier in publications – we thank each one. We further gratefully acknowledge the support of Marjan S. Rupnik, PhD, Professor of Physiology, Institute of Physiology, Center for Physiology and Pharmacology, Medical University of Vienna, Austria, for pre-submission review of the literature and our fruitful discussions.

Conflict of interest

Björn L.D.M. Brücher is Editor-in-Chief in Life Sciences-Medicine of *4open* by EDP Sciences. Ijaz S. Jamall is Senior Editorial Board member in Life Sciences-Medicine of *4open* by EDP Sciences. The authors, of their own initiative, suggested to the Managing Editorial to perform a transparent peer-review of their submittals. Neither author took any action to influence the standard submission and peer-review process, and report no conflict of interest. The authors alone are responsible for the content and writing of the manuscript of this Special Issue. This manuscript contains original material that has not previously been published. Both authors contributed to the discussion on its contents and approved the manuscript.

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Cite this article as: Brücher BLDM, Jamall IS. (2019), Undervalued ubiquitous proteins. 4open, 2, 7.