Roles of tetraspanin proteins in cell and tumor biology

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Tetraspanin protein family and its web

In the human proteome, there are thirty-three proteins composing the tetraspanin (Tspan) family, which are a group of highly hydrophobic membrane proteins defined by their structural characteristics (Figure 1). Tetraspanins have four transmembrane domains with short intra-cytosolic N- and C-terminal regions, and two extracellular (EC) loops (Tarrant et al., 2003). The large EC2 loop has distinctive characteristics, such as a conserved CCG motif and conserved cysteines permitted the identification of a protein signature (Shoham et al., 2006), so that three tetraspanin subgroups are identified based on their folding patterns (Seigneuret et al., 2001). The hydrophobic transmembrane regions also contain conserved polar residues (Figure 1). The short C-terminal region is likely to provide a link to intracellular signaling molecules (Stipp et al., 2003).

Figure 1

[Diagram showing the structure of tetraspanin proteins with labeled EC1 and EC2 regions, and percentages for various amino acids and residues.]
Tetraspanin biology should be considered as a compartmentalized system (Levy and Shoham, 2005). The tetraspanin web is a complex containing several tetraspanins interacting among themselves on the membrane, forming a core that can interact with many different molecules; thus the composition of individual complexes is very likely to determine different biological effects (Lazo, 2007), making it a compartmentalized system. Most of the knowledge on this web was obtained from a small number of tetraspanins, mainly CD9, CD81, CD82 and CD151 (Hemler, 2005). CD53, CD63 and CD37 have also been detected in complexes, and the remaining tetraspanins have not been studied in this context. Their combination permits a large variability, forming platforms for associated proteins (Levy and Shoham, 2005), which is very likely to be more important biologically than individual components. These proteins are expressed in most cell types (Wright et al., 2004), but most of the functional information has been obtained in cells of the hematopoietic system or epithelial cells (Hemler, 2005).

The tetraspanin partners in the web

Individual tetraspanin proteins can interact with several different types of proteins (Levy and Shoham, 2005), most of which play a receptor role, or alternatively couple receptors to signalling pathways. These interacting proteins range from membrane receptors, adhesion molecules to signal transduction molecules (Table 1).
Some of these protein-protein interactions are restricted to a specific tetraspanin protein. The combination of tetraspanins and the proteins listed in Table 1 suggests there are multiple different combinations between tetraspanins and their associated proteins. Although some combinations are specific, clearly many others remain to be identified. This heterogeneity of tetraspanin interactions with a variety of membrane proteins is likely to determine the biological role of tetraspanins as costimulatory molecules.

**Interactions with integrins, relevance to cellular adhesion**
Individual interactions between tetraspanins and integrins but are the most extensively studied interaction, but their web context was not considered (Berditchevski, 2001). However, despite the relevance of integrins in processes such as adhesion to extracellular matrix, cell motility, invasion and angiogenesis (Janes and Watt, 2006; Watt, 2002), the functional consequences of these interactions have received relatively little attention, perhaps because no tetraspanin ligand has so far been identified.

The main integrin found associated are those containing the β1 chain, mostly combined with α3, α4 or α6, in most cell types; and less frequently α2 and α5 (Berditchevski, 2001). The β1 chain is a major component of the attachment to the extracellular matrix (Hemler and Lobb, 1995), and signals by the activation of the integrin-linked kinase (ILK) (Dedhar, 2000). Some of these interactions have been reported for a specific tetraspanin, as is the case of α1β1 with CD9, but others as α4β1 were detected associated to CD9, CD53, CD81, CD82 or CD151. A direct interaction has only been demonstrated for CD151-α3β1 (Yauch et al., 2000). In general it can be concluded that one α integrin can bind to more than one type of tetraspanin. Although the β chain also contributes to the interaction, as exemplified by CD151 that interacts with α6β1 and α6β4 (Berditchevski et al., 1996). These CD151-integrin interactions strengthened the attachment to the extracellular matrix (Nishiuchi et al., 2005), but if they are functionally different depending on cell type, lymphoid or epithelial, is not known.

The tetraspanin complex with integrins is in low affinity conformation, and changes in affinity do not alter the integrin-tetraspanin interaction and integrin activation does not affect their tetraspanin interaction (Berditchevski, 2001), but tetraspanins appear to affect the post-ligand effects such as modulating actin dynamics, reflected in migration and cell adhesion properties. The tetraspanin-integrin complexes a might provide spatial cues for cellular polarization (Yanez-Mo et al., 2001).

Growth factor receptors and other membrane receptors

Growth factor receptors is a major group of Tspan interacting proteins, the receptors belong to different types (Table 1) including those with immunoglobulin domains, particularly those of the EWI family, but without considering their supramolecular organization, which can affect the magnitude or specificity of their effects and the functional consequences of any of them are unknown.

Regarding growth factor receptors with tyrosine-kinase activity, CD9 interacts with the HB-EGF receptor (Lagaudriere-Gesbert et al., 1997) and. c-Met/HGF-R (hepatocyte growth factor receptor), the receptor for the scatter factor (SF) or HGF that is implicated in epithelial-mesenchimal transition, a fundamental process in the dissemination of tumor cells (Trusolino and Comoglio, 2002) c-Met interacts with CD82 (Sridhar and Miranti, 2006). The interaction of the ganglioside GM2 with the CD82-c-Met inhibits its cross-talk with integrin signaling, and reduces c-Met activation signal (Todeschini et al., 2008). In epithelial cells CD9 interacts with epithelial cell adhesion molecule (Ep-CAM) (Le Naour et al., 2006). But the functional consequences of interactions between different tetraspanins and cadherins have not yet been performed.

It can be concluded that our knowledge on tetraspanin effects on signals initiated in interacting growth factor receptors is rather limited.

Membrane proteins

Proteins of the HLA family, both class II and class I, constitute a major group of proteins associated with tetraspanins (Lagaudriere-Gesbert et al., 1997; Szollosi et al., 1996).The most characterized is the interaction with class II antigens, but class I have also been detected (Berditchevski and Odintsova, 2007; Engering and Pieters, 2001; Szollosi et al., 1996), particularly with CD53, CD37 or CD81 (Angelisova et al., 1994). However, if tetraspanin proteins modulate signals or functions mediated by these HLA antigens has not been characterized, but are likely to affect antigen presentation (Berditchevski and Odintsova, 2007). In dendritic cells the lateral interaction between CD9 and MHC class II antigen facilitated T-cell activation (Unternaehrer et al., 2007). It will be important to determine their functional consequences in tumor cells were HLA antigens expression is frequently downregulated to facility immune evasion.

Intracellular signaling molecules

Tetraspanins are considered as molecular facilitators because they participate, or modulate, several signaling and biological processes (Maeker et al., 1997), detected in very heterogeneous cell types, but their implication is clear; tetraspanins can influence intracellular signaling, directly or indirectly, and
thus can modulate signals initiated in other membrane receptors that are present on the Tspan web. Due to the lack of any known ligand, most signals have been studied using specific monoclonal antibodies. In this regard CD9, CD82, CD81 and CD53 are the best-characterized antigens (Boucheix and Rubinstein, 2001). Among signals detected in response to tetraspanin antigen ligation by monoclonal antibodies were calcium mobilization by CD9, CD53, CD81 or CD82, protein kinase C activation, increased levels of diacylglycerol, activation of phosphatidylinositol 3-kinase (PI 3K) and phospholipase Cy (Boucheix and Rubinstein, 2001).

Another component of tetraspanin signaling is a consequence of direct physical interaction between some tetraspanins, such as CD151, and type II phosphatidylinositol 4-kinase (PI 4K); in this case the tetraspanin functions as the connector between the associated integrin and the PI 4K molecule (Berditchevski et al., 1997; Claas et al., 2001). Only some tetraspanins, CD9, CD63, CD81, A15 and CD151 are associated with PI 4K, but not others such as CD82, CD53 or CD37; and their interaction does not require previous binding to an integrin, therefore it may be mediated by a not yet identified protein, and will have functional consequences depending on the pattern of expression and integration in the tetraspanin web in different cell types. All these effects have been reported in very heterogeneous cell types. But the implication is clear; tetraspanins can influence intracellular signalling, directly or indirectly, and thus can modulate signals initiated in other membrane receptors. CD53 ligation activates protein kinase C (PKC) (Barcia et al., 1996; Bosca and Lazo, 1994; Lazo et al., 1997); and later it was demonstrated that following cell stimulation, PKC binds to the intracellular side of CD9, CD53, CD81, CD82, and CD151 (Zhang et al., 2001), this bound PKC was able to phosphorylate the integrin α3 subunit interacting with CD151. Also CD53 ligation could transiently activate the c-jun NH2-terminal kinase (JNK) and c-Jun dependent transcription (Yunta et al., 2002). In renal mesangial cells the ligation of CD53 induced a proliferative response mediated by the extracellular-regulated kinases, ERK1 and ERK2 (Yunta et al., 2003). Furthermore, CD53 and CD63 have been found associated with a tyrosine phosphatase (CD45) that dephosphorylates lck (Carmo and Wright, 1995).

The tetraspanin web is regulated by lipids

Palmitoylation determines the formation of cholesterol rich microdomains

Membrane proteins can be covalently modified by palmitoylation that can control their association and organization in different cellular membranes. The tetraspanins CD9, CD37, CD53, CD63, CD81, CD82 and CD151 are palmitoylated molecules (Charrin et al., 2002), that occurs in intracellular cysteines; and which is a requirement for their association with cholesterol complexes (Charrin et al., 2003). The assembly of the tetraspanin web is started in the Golgi, where homodimers, as well as heterodimers, of CD9, CD81, or CD151, constituting intermediate building blocks in the assembly of the tetraspanin web (Kovalenko et al., 2004). Palmitoylated tetraspanins appeared to be important for assembly of the web, favoring association with other tetraspanins and their associated proteins (Berditchevski et al., 2002; Yang et al., 2002). Palmitoylated CD9, CD81, and CD63 colocalize with palmitoylated integrin β4, which promoted the incorporation of CD151 to these tetraspanin complexes (Yang et al., 2004). There are two types of complexes, those with palmitoylated tetraspanins that facilitate their association with integrins and integration in cholesterol-rich fractions, and those non-palmitoylated tetraspanins that are accessible to binding with different signaling molecules, such as 14-3-3, p130 (CAS) or EWI proteins among others. These two alternative signaling complexes are summarized in Fig.2.
Palmitoylation of CD9 promotes interaction with integrins and association with other tetraspanins, CD81 and CD53. Mutations in all palmitoylation residues CD9 (Charrin et al., 2002) or CD151 (Yang et al., 2002) resulted in a more diffuse distribution and prevented their association with cholesterol. Un-palmitoylated CD9 is freer and has an enhanced binding to EWI-2 and EWI-F (Yang et al., 2006). The loss of palmitoylation did not affect spreading on extracellular matrix, but these cells have a larger number of focal adhesions, and an increase in adhesion-induced phosphorylation of Akt, without affecting activation of FAK or ERK1/2 (Berditchevski et al., 2002).

Palmitoylation also controls the association between tetraspanins and intracellular signaling molecules. In these complexes, tetraspanin ligation increased phosphorylation of signaling molecules such as vav, and effect lost by treatment with cholesterol disrupting detergents (Charrin et al., 2003). In B-cells the coligation of the B-cell receptor (BCR) with CD19/CD21/CD81 promoted CD81 palmitoylation and stabilization of the complex within a cholesterol rich fraction (Cherukuri et al., 2004). CD82 palmitoylation is necessary for mobility and invasion of PC13 cells, and loss of palmitoylation resulted in abolishment of these properties, and in regaining interaction with the p130 (CAS)-CrkII signaling complex (Zhou et al., 2004), also detected in CD9 (Yang et al., 2004).

Palmitoylation was regulated by the cellular redox state, and under oxidative stress palmitoylation is inhibited favoring signaling by 14-3-3 adaptor proteins (Clark et al., 2004), thus not palmitoylated CD81 was constitutively bound to 14-3-3 protein, a serine/threonine binding protein (Clark et al., 2004).

Gangliosides can regulate the composition of the tetraspanin web

Gangliosides are complex glycolipids which contain a branched chain of as many as seven sugar residues. Several specific interactions of gangliosides with tetraspanins have been reported. Thus GM3 ganglioside preferentially interacts with CD9 (Kawakami et al., 2002; Mitsuzuka et al., 2005) and CD81 (Toledo et al., 2004), reducing MAPK activation initiated in FGFR (Toledo et al., 2004). GM3, promotes the association of CD9 with the α3 integrin (Kawakami et al., 2002) or &alpha5; inhibiting cell motility (Miura et al., 2004). The GM2 ganglioside is mainly associated with CD82 (Odintsova et al., 2006; Todeschini et al., 2008), and GD2/GD3 gangliosides interacting with CD151 (Thorne et al., 2007) and CD82 inhibited cell motility (Todeschini et al., 2008).

Dynamics of tetraspanin microdomains: cell-specific complexes
The web assembly of tetraspanins and their specific interactions can be interpreted within the general framework of the dynamics of a complex with the potential for a very high functional heterogeneity (Fig.2). In this system there is a double level to increase complexity, the participation of the tetraspanins in the core, and the type and number of associated proteins. Thus diversity in the combination of proteins permits a very large flexibility which can determine functional differences depending on cell type. Therefore, tetraspanin complexes in specific cell types can be very different despite sharing several of their components. In that way the association of tetraspanin-membrane receptor may exist either as isolated complexes on cell surfaces, or forming part of a larger tetraspanin-core complex. Thus, the association-dissociation kinetics represents an important level of regulation, where palmitoylation and redox state play a major role, but these properties have not yet been characterized in detail in any system. Initiation of cell signals is very likely to be different if activated by either free molecules, in heterodimers, or a larger complex, such as the tetraspanin web.

**Contribution of Tetraspanins to tumor biology: cell adhesion and motility**

**CD151.** CD151 is mainly localized to the basal and lateral junctions of endothelial cells (Berditchevski and Odintsova, 1999) and blocking antibodies increased their adhesion to the ECM and reduced their rate of invasion in collagen gels (Yanez-Mo et al., 1998). In migrating keratinocytes and breast cancer cells CD9, CD81, CD151 were involved in transient interactions with the substrate before a more stable interaction could be formed by attachment structures due to lamellipodia formation (Penas et al., 2000). These structures were both did not contain elements of the cytoskeleton, and colocalized with MARCKS, which are substrates of PKC that regulates cytoskeleton reorganization during migration (Berditchevski and Odintsova, 1999). In human skin, CD151 was clustered at the basal cell colocalizing with laminin 5 (Lagaudriere-Gesbert et al., 1997; Yamada et al., 2008) connecting focal adhesion with actin filaments as part of hemidesmosomes (Sterk et al., 2000). In polarized epithelial cells, CD9, CD151 and CD81 also localize with cadherins at lateral cell-cell contacts although the effect of antibodies is cadherin-independent. Overexpression of CD151 resulted in increased motility, and enhanced expression of matrix metalloproteinase-9 (MMP-9) and invasiveness (Hong et al., 2006); probably as a result of activating pathways mediated by small GTPases (Shigeta et al., 2003). CD151 knock-down in primary melanocytes resulted in a loss of motility (Garcia-Lopez et al., 2007), effects that are reversed by CD151 reexpression (Winterwood et al., 2006). The dissociation of CD151 from laminin-binding integrins permitted migration of epithelial cells (Chometon et al., 2006). These data on signaling and motility clearly implicate CD151 in cell adhesion and dissemination. The blocking of CD151 with an antibody is able to prevent tumor intravasation and metastasis (Zijlstra et al., 2008).

**CD82.** CD82 functions as a link between the actin cytoskeleton and membrane raft domains, inducing stable adhesion, spreading and development of membrane extensions. CD82 effects on actin polymerization depend on its association with the ECM and involves src kinases, Vav1, and p56 lck (Delaguillaumie et al., 2002; Lagaudriere-Gesbert et al., 1998). The depletion of gangliosides also destabilizes CD82 complexes (Ono et al., 1999), reducing interaction with CD151 and increasing the interaction with EGFR (Odintsova et al., 2006) and c-Met (Todeschini et al., 2007). All these effects are severely affected by cholesterol depletion (Delaguillaumie et al., 2004). Overexpression of CD82 might contribute to tumor invasion by inhibiting the cross-talk between integrins and Met and src activation and phosphorylation of its downstream targets, p130Cas and FAK (Sridhar and Miranti, 2006; Zhang et al., 2003). Inhibition of c-Met or Src reduced invasion to the same extent as CD82 e(Sridhar and Miranti, 2006). High levels of CD82 correlate with a lower invasion potential in prostate (Zhang et al., 2003), lung (Adachi et al., 1996), esophageal cancer (Uchida et al., 1999) and by its overexpression in multiple myeloma cell lines (Tohami et al., 2007).

CD82 surface expression is up-regulated by several cytokines such as interleukin-1 beta (IL-1 β), IL-4, IL-6, IL-13, interferon-gamma, tumor necrosis factor-a antigen (Lebel-Binay et al., 1995b). Co-ligation of CD82 and Fc receptors induces an increase in calcium level mediated by phospholipase C (PLC)-induced PtdIns(1,4,5)P3 second messenger followed by a more stable change, linked to extracellular calcium entry (Lebel-Binay et al., 1995b). In Jurkat cells stimulated of with anti-CD82 and anti-CD3 mAbs implicates different transcription factors such as NF-AT, AP-1, and NF-kB (Iwata et al., 2002), with increased production of IL-2; and cells become adherent developing dendritic extensions, cell proliferation is arrested (Lebel-Binay et al., 1995a). The interaction of CD82 with DARC (duffy antigen receptor for chemokines) a in on prostate and endothelial cells has been identified as a binding partner of CD82 cells (Bandyopadhyay et al., 2006), makes them to enter senescence (Iizumi et al., 2007).

**CD9.** The association of CD9 with the transmembrane region of TGF-α resulted in the induction of EGFR activation and cellular proliferation (Shi et al., 2000). Also, the metalloprotease ADAM10
promotes the association of CD9 with HG-EGF (Yan et al., 2002). But CD9 has been associated with control of cell motility. Functionally antibodies anti-CD9 inhibited transmigration of melanoma cells (Longo et al., 2001). In primary melanocytes where reduction of CD9 by siRNA resulted in loss of motility (Garcia-Lopez et al., 2005). Cell motility dependent on binding to laminin-5 is inhibited by the interaction of CD9 with the GM3 ganglioside (Kawakami et al., 2002). All these data suggested that CD9 as well as CD81 loss are likely to promote tumor dissemination. In agreement with this potential role, an inverse correlation between CD9 level and invasiveness has been reported in melanomas (Si and Hersey, 1993), breast cancer (Huang et al., 1998), oral squamous cell carcinomas (Kusukawa et al., 2001), ovarian carcinoma (Houle et al., 2002), and cervical carcinomas (Sauer et al., 2003b).

**CD81.** The ligation of CD81 initially had an antiproliferative effect, and regulated the intracellular thiol levels (Schick et al., 1993), forming part of the CD19/CD21 signaling complex on B-cells (Behr and Schriever, 1995). CD81 and CD151 tetraspanin molecules are components of the endothelial lateral junctions implicated in the regulation of cell motility, either directly or by modulation of the function of the associated integrin heterodimers (Yanez-Mo et al., 1998); and CD81 was associated with adhesion and motility in lymphocytes (Levy et al., 1998). The link between CD81 and the actin cytoskeleton seems to be mediated by EWI-2 and EWI-F (Sala-Valdes et al., 2006). CD81 overexpression reduces viability and motility in multiple myeloma cell lines (Tohami et al., 2007).

**CD63.** CD63 antigen is mostly detected at a very high concentration in endosomal particles; but it is also presented on cell surfaces. The C-terminal intracellular region of CD63 interacts with the PDZ domain of syntenin-1, a molecule that is implicated in regulation of endocytosis and slows down CD63 internalization (Latsyheva et al., 2006). CD63 expression on cell surface affects tumor dissemination. The loss of CD63 was the first tetraspanin to be related with a very high invasive potential in melanomas, where an inverse correlation between CD63 levels and metastatic potential was identified (Hotta et al., 1988; Hotta et al., 1989), and its reexpression in melanoma cells reduced its invasion potential (Radford et al., 1995). A similar correlation has been reported in a colon carcinoma cell line (Sordat et al., 2002).

**CD53: Radioresistance and effects on redox state.** The CD53 ligation antigen with specific antibodies stimulates several processes such as the induction of nitric oxide synthase (Bosca and Lazo, 1994) in macrophages, homotypic cell adhesion in B-cell lymphomas (Lazo et al., 1997), or DNA synthesis in mesangial cells (Yunta et al., 2003), all of them on PKC activation. Part of the signal is also transmitted by the JNK system and has a protective effect on apoptosis in Jurkat cells (Yunta and Lazo, 2003).

CD53, CD82 and CD81 interact with gamma-glutamyl transpeptidase (GGT) a regulator of the intracellular redox state by modulating level of glutathione (Nichols et al., 1998). This is a very interesting observation because the mechanism by which cells are killed by radiation therapy is based on its ability to generate free radicals in the cell; and is therefore strongly dependent on the intracellular redox state. Very high overexpression of CD53 is one of the main markers of radioresistant cells (Voehringer et al., 2000), resulting in an increase in the intracellular level of glutathione, which has anti oxidant properties and thus counteracts the radiation effect facilitating cell survival (Voehringer et al., 2000).

**Patterns of tetraspanin protein expression in normal and stem cells**

**Tetraspanin surface expression in hematopoietic cells**

The only overall picture of tetraspanin surface expression has been obtained in human B-cell maturation, in which the relative surface levels of six tetraspanins (CD9, CD37, CD53, CD63 and CD81), and their interacting proteins (CD19, CD21, and HLA-DR) was determined (Barrena et al., 2005b). This study identified three different combinations based on developmental stage: I) early bone marrow (BM) CD10+ B-cell precursors have high levels of CD81 and CD9 and relatively very low level of CD53, and negativity for CD37; II) mature/peripheral B-lymphocytes (CD10+) there is down-regulation of CD9/CD81 and up-regulation of CD53/CD37; III) in plasma cells that have passed through secondary lymphoid tissues and reentered the BM there is CD9 re-expression and CD37 down-regulation, but maintain the CD53 expression. These distinct patterns of tetraspanin expression may reflect the occurrence of different cellular interactions and homing properties during B-cell maturation. (Barrena et al., 2005b).

Although precursors of lymphoid cells express relatively higher levels of CD9, they also express CD53 and CD63 intracellularly located in endosomes, two proteins that in CD133+ stem cell population are distributed asymmetrically (Beckmann et al., 2007), a hallmark of stem cells, but its significance is unknown.
Tetraspanin proteins in epithelial cells

A systematic approach to detect six tetraspanin proteins, CD9, CD37, CD53, CD63, CD81, and CD82, in the gastrointestinal (GI) tract has been performed. Two of them, CD9 and CD82 were expressed at similarly high levels throughout the GI tract, from esophagus to colon. CD63 expression was more restricted, ranging from distal stomach to colon. CD81 was detected only in basal layers of the esophagus. CD53 was barely detected and no expression of CD37 was observed (Okochi et al., 1999). These differences suggest that the organization of the tetraspanin web can present major variations depending on its localization in the GI; but their functional significance is not known.

Tetraspanin proteins have also been used to attempt to identify epithelial precursor cells in the airway tract, which is severely damaged in diseases such as cystic fibrosis. In the basal cells of the trachea there is compartment of stem and transit amplifying cells. A marker of early stages is the detection of CD151 in combination with TF (Tissue factor) antigens. Therefore, tracheal cells positive for CD151/TF were able to proliferate and reconstitute a fully differentiated epithelium in rat with epithelium-denuded trachea. These cells were also positive for telomerase activity, which is considered a marker for the transit amplifying population. Cells of the columnar epithelium, CD151/TF negative were unable to proliferate or reconstitute the epithelium and have no telomerase activity. These data suggest that adult basal cells, CD151 positive, are present in the amplification compartment of the epithelium and have some regenerative potential (Hajj et al., 2006). It is not known if in other epithelial cells the situation is similar.

In the basal layer of normal squamous cervical epithelium there is a very high expression of CD9; which is down-regulated in squamous cervical carcinomas correlating with stage, but surprisingly as the tumor progresses there is a re-expression of CD9 as it becomes more vascularized, what might be an important element to permit tumor dissemination (Sauer et al., 2003b), and might reflect an interaction with vascular cells not yet identified.

Tetraspanins in human cancer

Most the information on expression of multiple tetraspanin proteins is a consequence of the information obtained using expression microarray in the analysis of different types of human cancer. These studies provide information on two aspects, the antigens expressed based on a given phenotype, and the relative change in the pattern as a function of differentiation or tumor phenotype, which indicate that they are functionally different.

Tetraspanin proteins in B-cell malignancies

The cell surface expression of four tetraspanin antigens and associated proteins has been studied in sixty-seven cases of B-cell malignancies (Barrena et al., 2005b). Hierarchical clustering analysis of flow cytometry immunophenotypic data showed a good correlation between the tumor differentiation stage and the pattern of tetraspanin expression (Barrena et al., 2005b). Mature/peripheral B-cell leukemias and lymphomas expressed high levels of CD37 and CD53; while those derived from BCP-ALL (acute lymphocytic leukemia), and clonal plasma cells (PC) coexpressed CD9 with either CD81 or CD53, respectively. Despite these phenotypic similarities, variable levels of expression of one or more of these proteins were frequently expressed and of these phenotypic aberrations were common to most patients within a specific disease group. The differences in the pattern of tetraspanin surface expression can be used to discriminate two different lymphomas in an individual patient (Barrena et al., 2005a). In B-CLL, the pattern of expression of CD9 and CD53 tetraspanins was associated with the pattern of in vivo tissue involvement. Thus, abnormally high reactivity for CD53 was associated with greater PB and lymph node infiltration. Previously it was demonstrated that ligation of CD53 antigen protects lymphoid cells from apoptosis (Yunta and Lazo, 2003), an important property for mature/peripheral memory lymphocytes. Therefore, overexpression of CD53 could render B-CLL (chronic lymphocytic leukemia) cells more adapted to survive in peripheral blood (PB) and lymph nodes. In contrast, reduced CD9 expression on B-CLL cells has been associated to a higher bone marrow (BM) involvement. CD9 also functions as a motility/migration brake (Ono et al., 1999), and this might explain the correlation detected between CD9 expression and the pattern of BM involvement.

In multiple myelomas (MM), there is CD9 expression in non active MM, while in active and aggressive MM there is an epigenetic silencing of CD9 gene expression (De Bruyne et al., 2008).

Tetraspanin proteins in carcinomas
Information on expression in carcinomas is derived mostly or from gene expression arrays and from determining few protein antigens; and functional information has been obtained from tumor cell lines. Tetraspanins have received little attention in human carcinomas but some information is emerging form three different lines of work.

The alternative expression of some tetraspanin antigens permits the identification of subgroups in different types of human cancer. The coordinated expression of tetraspanin initially identified in B-cells (previous section) appears to be more general. In kidney cancer, high expression of CD53 and CD37 inversely correlated with respect to CD9 expression (low) in conventional renal cell carcinomas of clear cells and in papillary carcinomas, but not in other types such as granular carcinomas in which CD9 expression is very high (Higgins et al., 2003). Also, in melanomas there is no CD53 and CD37 expression and express varying levels of CD9, the latter is inversely correlated with metastatic potential (Si and Hersey, 1993), a pattern consistent with a higher probability of infiltration in lymph nodes (Barrena et al., 2005b).

The loss of CD9 antigen has been correlated with higher motility and metastatic potential of tumor cells from lung (Higashiyama et al., 1995), esophageal (Uchida et al., 1999), oral (Kusukawa et al., 2001), ovarian (Houle et al., 2002), cervical (Sauer et al., 2003b), gastric (Hori et al., 2004) carcinomas. In the basal layer of the normal squamous epithelium of the uterine cervix CD9 is strongly expressed, but in invasive carcinomas is downregulated. However in some areas there is a re-expression of CD9 that were correlated with lymphangiosis. This cluster of CD9 might be an indicator of a higher risk of recurrence, since CD9 plays a role in transendothelial migration (Sauer et al., 2003b). In bladder cancer cell lines GM3 in glycosynapse 3 has a dual functional role. The first one modulates the interaction between α3 integrin and CD9; the second is to activate or inhibit the activity of c-src. Functionally high levels of GM3 reduce motility and invasiveness, while low levels have the opposite effect (Mitsuizuka et al., 2005).

In melanomas CD63, one of the original tetraspanins was identified in melanomas, where its levels inversely correlated with metastatic potential (Hotta et al., 1988), and in cell lines its overexpression suppresses the malignant phenotype (Hotta et al., 1991).

The expression of four tetraspanin proteins, CD9, CD63, CD82 and CD151 was studied in breast carcinoma cell lines with different invasive capabilities in in vitro assays. The expression of three of them, CD9, CD63 and CD151 appeared to be coordinated by a common mechanism, and low levels clearly predicted their invasive potential, particularly for CD63 (Sauer et al., 2003a).

Tetraspanin expression has been studied in a model of colon carcinoma with cell lines derived from primary tumors and two from metastasis. Thirty-two proteins were detected by a proteomic approach and included integrins, proteins with Ig domains, CD44, and epithelial cell adhesion molecule (EpCAM), membrane proteases (ADAM10, TADG-15, and CD26/dipeptidyl peptidase IV), and signaling proteins (heterotrimeric G proteins). Also some differences were identified, particularly the Cg-029 tetraspanin antigen in the metastasis, that was almost absent in primary tumors, but very high in normal colon (Le Naour et al., 2006).

In thyroid tumors CD82 is highly expressed in benign goiter, but expression was significantly reduced in carcinomas and were reduced even further in metastasis; in these tumors there were no changes in the expression of CD63 (Chen et al., 2004).

Some prostate carcinomas have downregulated CD9 and CD53 in those cases with high levels of CD151; CD9 and CD53 are upregulated in another group of prostate carcinomas (Lapointe et al., 2001). In these tumors CD9 and CD53 expression seems to be positively coordinated, which is the opposite of what occurs has been detected in other cell types. In low-grade prostate cancer the survival rate was higher in those cases were CD151 levels were lower, and in this study CD151 had a better prediction value than histological (Gleason) grade (Ang et al., 2004). In murine prostate cancer cells can attach to vascular endothelial cells through DARC, and this interaction inhibits proliferation and induces senescence by expression of TBX2 and p21 (Bandyopadhyay et al., 2006). The role of CD82 as a metastasis suppressor is compromised in DARC knockout mice. All these data suggests that the interaction DARC-CD82 is essential for the metastasis suppressor role of CD82 (Bandyopadhyay et al., 2006). It would be interesting to know if a similar interaction is found for other tetraspanin proteins that also behave as metastasis suppressors.

Bladder cancer represents a particular tumor due to its mechanical properties. The expression of uroplakins, an antigen that seals the bladder epithelium, can be used to identify the type of tumors and its severity. Uroplakin II is mainly expressed in transitional bladder carcinomas but not in squamous cell carcinomas and can be use to monitor for circulating cancer cells and in metastasis (Olsburgh et al., 2003).
In breast cancer CD151 is overexpressed in a third of the cases and correlates with high grade, and estrogen receptor negative tumors. The effect of CD151 is mediated by the upregulation of signals by integrin α6 through FAK, Rac1, and Ick (Yang et al., 2008).

The future of tetraspanins in cancer biology

Despite the very heterogeneous information on tetraspanin proteins in relation to cancer, it is very likely that patterns of expression of these proteins will affect the behavior of tumor cells with respect to signaling by growth factors, cell motility and sensitivity to therapy, which will be identified when these studies are performed. The regulatory role played by palmitoylation and gangliosides will require further characterization since they modulate cell signaling by associated growth factor receptors. It is expected that in the future these proteins will attract more attention and be studied in the proper context within tumor biology, since they are likely to play an important role in conferring specificity to many biological effects.

Although the basic processes where tetraspanin proteins play a role have already been outlined, their specific participation in these processes and in different cell types will require a systems approach where the multiplicity of components, their relatives levels, and localization are taken simultaneously into account thus generating a specific cell behavior. Their systematic determination in specific tumors is very likely to predict, and/or identify, their metastatic potential.

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