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Implication of the tetraspanin CD9 in the immune system and cancer

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IMPLICACIÓN DE LA TETRASPANINA CD9 EN EL SISTEMA INMUNE Y EN EL CÁNCER

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RESUMEN

Las tetraspaninas son moléculas de la superficie celular de amplia distribución en los organismos eucarióticos. Poseen como característica estructural peculiar cuatro dominios transmembranales, regiones N- y C-terminales intracitoplásmicas, y dos lazos extracelulares de distinto tamaño. También poseen un motivo de secuencia CCG en el lazo extracelular mayor, así como residuos polares conservados en los dominios transmembranales. Las células sanguíneas de los mamíferos expresan combinaciones peculiares de distintas tetraspaninas, incluyendo los antígenos de diferenciación CD9, CD37, CD53, CD81/TAPA-1, CD82, CD151/PETA-3 y CD231/TALLA1.

En este trabajo se resumen la estructura y las interacciones de sus regiones citoplásmicas con proteínas del citoesqueleto y señalizadoras, como la proteína cinasa C (PKC) o la Fosfatidil-Inositol 4-cinasa (PI4-K). Sus interacciones específicas con otras tetraspaninas, con integrinas, antígenos de histocompatibilidad, y miembros de la superfamilia de las inmunoglobulinas son también revisadas.

Las tetraspaninas son proteínas "adaptadoras" o "facilitadoras". Al formar parte de complejos moleculares, modulan funciones celulares clave que incluyen la fusión celular, la adhesión, la migración, la diferenciación y la transducción de señales. Las tetraspaninas se organizan en una red con distintos niveles de asociación, determinados por su resistencia a la solubilización por detergentes. En concreto, se analizan las tetraspaninas como reguladoras del Sistema Inmunitario gracias a sus interacciones con los receptores de antígeno de los linfocitos T y B, las moléculas de histocompatibilidad de clase I y clase II, y los co-receptores CD2, CD4, CD5, CD8 y CD19. Por último, se revisa detalladamente el papel de la tetraspanina CD9 en la función de las células linfoides y mieloides, su relevancia en infecciones como el HIV, y la importancia de su asociación con integrinas en la progresión cancerosa.

PALABRAS CLAVE: Tetraspaninas/ Integrinas/ HIV/ Cáncer/ CD9/ CD37/ CD53/ CD81/ TAPA-1/ CD82/ CD151/PETA-3/ CD231/TALLA1.

ABSTRACT

Tetraspanins are cell surface proteins widely distributed in eukaryotic organisms. They characteristically span four times the plasma membrane, have intracellular N and C terminal regions, and two extracellular loops of unequal size. Tetraspanins also possess a CCG motif in the large extracellular loop, and conserved polar residues in the transmembrane domains. Mammalian blood cells express different sets of tetraspanins including the differentiation antigens CD9, CD37, CD53, CD81/TAPA-1, CD82, CD151/PETA-3 and CD231/TALLA1.

Here, tetraspanin structure and their cytoplasmic tail interactions with cytoskeletal and signalling proteins like Protein kinase C (PKC) or Phosphatidyl Inositol 4-kinase (PI4-K) are briefly summarized. The specific interactions with other cell surface proteins, forming complexes with other tetraspanins and members of the integrin family, MHC histocompatibility antigens, or members of the immunoglobulin superfamily are also reviewed.

Tetraspanins are considered as "adapter" or "facilitating" proteins and, through their participation in complexes, they modulate key cellular functions like cell fusion, adhesion, migration, differentiation and signal transduction. The organization of the tetraspanin web, based on different association levels determined by their resistance to detergent solubilization, is described. In particular, tetraspanins participating in the regulation of the Immune System through interactions with the B- and T-cell receptors, the class I and class II MHC antigens, and co-receptors such as CD2, CD4, CD5, CD8, or CD19 are analyzed. At last, the role of CD9 in myeloid and lymphoid cell function, its relevance to HIV infection, and the importance of tetraspanin association with integrins to cancer progression are described in detail.

KEY WORDS: Tetraspanins/ Integrin/ HIV/ Cancer/ CD9/ CD37/ CD53/ CD81/TAPA-1/ CD82/ CD151/PETA-3/ CD231/TALLA1.

INTRODUCTION

Tetraspanins are a family of cell surface proteins that span four times the plasma membrane, and whose N and C terminal regions are both intracellular, delimiting two extracellular domains of unequal size termed SEL (Short Extracellular Loop) or EC1 (Extracellular Domain 1) and LEL (Large Extracellular Loop) or EC2 (Extracellular Domain 2). There are many types of proteins that contain four transmembrane domains, but in order to belong to the tetraspanin family, they must fulfil several additional structural requirements. These are the presence of 4-6 conserved cysteines including the CCG (Cysteine-Cysteine-Glycine) motif in the LEL domain, that allow for the formation of two, and in some cases three, intramolecular disulfide bonds in this domain[1], as well as several conserved polar residues in the transmembrane domains. This protein superfamily is widely distributed in eukaryotic organisms, and members of this family have been found in fungi, worms, insects and mammals. Mammalian tetraspanins comprise 32 members that include the differentiation antigens CD9, CD37, CD53, CD81/TAPA-1, CD82, CD151/PETA-3 and CD231/TALLA1 that are expressed by different lineages of blood cells[1-4]. All nucleated cells express on their surface a repertoire of different tetraspanins.

STRUCTURAL ASPECTS OF TETRASPANINS

The generic topology of a tetraspanin molecule has been established by different types of studies and is illustrated in Figure 1. From a structural point of view, the two (or three) disulfide bonds within the LEL subdivide this domain into two regions, a constant and a variable region. The constant region contains three differentiated segments of α-helix (termed A, B and E helices) that constitute a potential dimerization surface present in all tetraspanins[5,6]. The variable region contains all the sites so far identified that are involved in lateral interactions among different tetraspanin molecules as well as between tetraspanins and other membrane proteins.

The first, third and fourth transmembrane domains of tetraspanins contain conserved polar residues that can form strong hydrogen bonds among them. These domains stabilize each tetraspanin molecule during its biosynthesis and in addition favour the associations among tetraspanin molecules and with other proteins; these associations are crucial for the assembling and maintenance of the tetraspanin web.

The cysteine residues in the cytoplasmic domains represent palmitoylation sites, which contribute to the interactions tetraspanin-tetraspanin[7,8]. The N and C-terminal cytoplasmic tails contain potential binding sites for cytoskeletal or signalling proteins, like Protein kinase C (PKC)[9] or Phosphatidyl Inositol 4-kinase (PI4-K)[10-12].

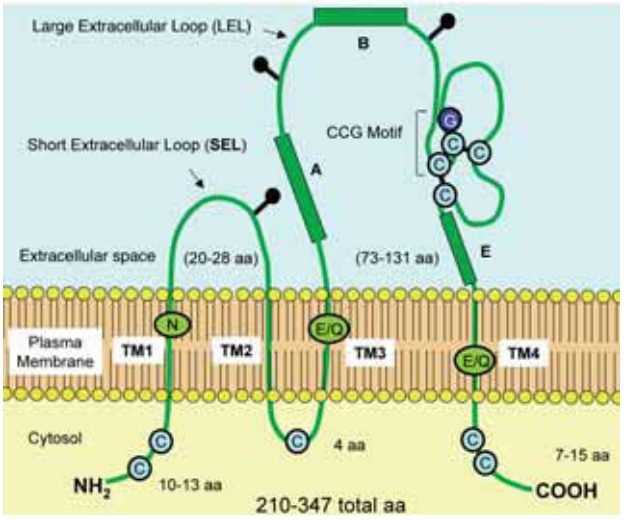

Figure 1. *Schematic general structure of tetraspanins. Tetraspanins present four transmembrane domains (TM) that contain conserved polar residues (green ovals) and delimit two extracellular loops of unequal size (Short Extracellular Loop SEL, and Large Extracellular Loop LEL, respectively). Both loops can contain one or several glycosylation sites (black rods), depending on the particular tetraspanin considered. The conserved cysteine residues are depicted by blue circles. Because of the formation of disulfide bonds (black lines) between the cysteines of the CCG motif and other conserved cysteines of the LEL, this domain folds and adopts a "mushroom" shape. The number of disulfide bonds ranges between 2 to 5 among the different tetraspanins. Several conserved cysteines are also present in the intracellular loop as well as in the N- and C-termini, which represent potential palmitoylation sites.*

DIFFERENT TYPES OF TETRASPANIN INTERACTIONS

One fundamental feature of tetraspanins is their high ability to establish specific interactions with other cell surface proteins, specially with other tetraspanins and with members of the integrin family, MHC histocompatibility antigens, and some members of the immunoglobulin superfamily[1,13,14]. Tetraspanins are accordingly considered as "adapter" or "facilitating" proteins characterized by their ability to organize networks of interactions among different cell surface proteins. These multiprotein complexes constitute authentic tetraspanin-enriched membrane microdomains, which have been termed "tetraspanin web". Through their participation in these complexes, tetraspanins have been implicated in key cellular functions like cell fusion, adhesion, migration, differentiation and signal transduction[1,2,4,15]. The organization of the tetraspanin web is based on different association levels (as illustrated in Figure 2). The first level comprises the primary or direct protein associations which are resistant to stringent detergents like Digitonin or Triton-X-100 and display high stoichiometry. Within this first level are included the interactions between a particular tetraspanin and one or few specific proteins, known as its "partners". A second level of organization includes the more abundant and indirect interactions, which