Discoidin Domain Receptors Role in Human Diseases

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Abstract

Discoidin Domain Receptor 1 and Discodin Domain Receptor 2 are the two only members of the DDR family. The DDR family is a Tyrosine Kinase Receptor (TKR) family with some peculiarities compared with other Tyrosine Kinase Receptors such as their natural ligand; which in this case is the fibrillar collagen; or the slow phosphorylation pattern. These peculiarities confer a special role to the receptors present in many diseases development processes as cancer, cirrhosis or lung fibrosis. In this review it is described the overview of the DDRs structure and their role in the different disease development and the possibility to consider them as therapeutic targets.

Keywords: cancer, cirrhosis, collagen receptor, metastasis, lung fibrosis, tyrosine kinase receptors

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Discoidin Domain Receptor 1 (DDR1)

DDR1 is expressed mainly during embrionary development and in the adult tissue in the lung, liver, colon, mammary glands, intestine and brain. Additionally it is very common to find DDR1 in many types of tumors such as: mammary, brain, lung or colon (Laval et al., 1995; Ram et al., 2005; Sanchez et al., 1994; Vogel et al., 2000, 2001; Weiner et al., 2000).

In the DDR1 deficient mice we can see the critical role of the receptor during the postnatal development and in the mammary gland formation (Vogel et al., 2001). It has been described an aberrant formation of the basal renal membrane and a reduction of the cell signalling capacity in the mesengial cells (Curat and Vogel, 2002). The muscular cells derived from DDR1 deficient mice show reduction of migration and chemiotactic capacity compared to with wild type ones. (Hou et al., 2001, 2002)

Discoidin Domain Receptor 2 (DDR2)

DDR2 is expresed in the muscle, heart, kidney, lung, liver and skin (Alves et al., 1995; Karn et al., 1993; Lai and Lemke, 1994; Olaso et al., 2001, 2002) Recently, it has been described also in the stromal cells surrounding the lung and ovarian tumors (Alves et al., 1995).

In vitro activation of DDR2 induces the expression of MMP1 and MMP (Olaso et al., 2001; Vogel et al., 1997), two enzymes involved in the remodelation of the extracellular matrix and tissue repair (Werb, 1997). The mitogenic response of some growth factors is regulated by metalloproteinases which control the availability of the receptor (Dong et al., 2004). The activation of DDR2 can degrade the extracellular matrix allowing some signalling cascades to interact with other signalling systems (Labrador et al., 2001). DDR2 phosphorylation occurs during hepatic stellate cell activation and it mediates MMP2 production in response to fibrillar collagen (Olaso et al., 2002). The activation of hepatic stellate cell and the induction of DDR2 by fibrillar collagen produce a feed-back effect resulting in more fibrillar collagen and stronger receptor phosphorylation (Olaso et al., 2002). DDR2 and MMP13 are overexpressed in arthritis, allowing cartilage degradation (Li et al., 2005). MMP1 is another metalloproteinase regulated by DDR2 (Vogel et al., 1997). Another important role of DDR2 is the mediation in the migration and proliferation of the hepatic stellate cells and fibroblast via MMP2 regulation (Olaso et al., 2001, 2002).

The DDR2 deficient mice are viable but they are dwarf and their long bones are shorter. This phenotype is due to a lower proliferation of condrocytes during bone growth.
The ddr1 gene was cloned for the first time in 1993 through hybridization of a consensus sequence of tyrosine kinase domain of Tyrosine Kinase Receptors (Johnson et al., 1993). The homologous gene in mouse called NEP was identified in the same year by Zerlin (1993). At the same time ddr1 was identified by other groups and was called like trc (Di Marco et al., 1993), PTK-3 (Sanchez et al., 1994), RTK6 (Laval et al., 1995), Cak (Perez et al., 1994) and MCK (Alves et al., 1995).

The human gene ddr1 is localized in the chromosome 6p21.3 near to HLA genes. In the mouse the gene ddr1 is localized in the chromosome 17. Both mouse and human ddr1 are composed by 17 exons. The extracellular domain is codified by 8 exons, 3 exons codify for the discoidin domain. An exon codifies for transmembrane domain, 3 for the juxtamembrane and 5 for the catalytic domain. Compared to other tyrosine kinase receptors, the juxtamembrane region of DDR1 is longer. 5 isoforms have been described so far generated by alternative splicing of the human ddr1 gene (Alves et al., 2001). The longer isoform is c with 919 aminoacids, b is shorter and lacks 6 aminoacids in the tyrosine kinase domain. The isoform d is the shortest one with only 509 aminoacids and lacks the tyrosine kinase domain. Finally, the isoform e has the tyrosine kinase domain but is not functional (Vogel et al., 2001).

Ddr2 was cloned in 1993 by Karn. At the same time it was cloned by some other groups calling it CCK-2 (Alves et al., 1995), Tyro 10 (Lai and Lemke, 1994), or TKT.

The human gene ddr2 is localized in the chromosome 1 in the region 1q12-q23 and in the mouse in the chromosome 1 in the region 190.0 cM. In humans it is composed by 19 exons and in mouse by 18.

Protein structure of DDRs

Extracellular region: discoidin domain and stalk region

The first 20 aminoacids are the signal peptide in both receptors. Then there is the discoidin domain constituted by 160 aminoacids. In between the discoidin domain and transmembrane domain there is the stalk region (aminoacids 199-412) (Curat et al., 2001). There is no homology of this region with other proteins. The interaction of the discoidin domain with the collagen requires the previousimerization of the receptor (Letinger, 2003), and this is not the classical concept of TKR activation where theimerization occurs after the ligand binding to the receptor (Schlessinger, 2000). The discoidin domain is essential for DDR binding to collagen because in this domain there are some critical residues like Ser-52-Thr57, Arg-105-Lys-112 and Ser-175 (Abdulhussein et al., 2004).

In the stalk region there are 3 important regions: the glicosilation region (Curat et al., 2001) for both receptors, the protease target sequence for DDR1 (Vogel, 2002), and for DDR2 an antigen sequence A5 (Lai and Lemke, 1994). The glicosilation of DDR1 is very important for the signalling and it occurs in the stalk region (Curat et al., 2001). After the binding to the collagen, DDR1 can be hydrolyzed in two regions: one region beta of 62 kDa attached to the membrane and another region alfa of 54 KDa which is soluble (Abdulhussein et al., 2004). The biological implication of this feature is still unknown but it may be that the alpha region binds collagens and regulates the union of collagen to the functional receptors.

Juxtamembrane domain

The juxtamembrane region of DDR1 and DDR2 is longer compared to the other TKR. There is an identical region for DDR1 and DDR2 in the exon 12 suggesting that it could be a critical region for signal transduction (Alves et al., 2001). In the case of DDR1 the juxtamembrane region has 176 aminoacids, is rich in prolines and contains 6 tyrosine residues that can be phosphorylation regions, and in the case of DDR2 is similar but shorter (Li et al., 2005). In this region there are some sequences very important for adaptors proteins. This region suffers the different splicing process in the case of DDR1 and is different depending on the isoforms (Alves et al., 1995). The isoform b has an insertion of an exon (exon 11, 111bp) and codified for 37 aminoacids (Playford et al., 1996). This region exists also in the DDR2 and contains the LXNPXY motif, which is important for Shc binding (Curat et al., 2001; Foehr et al., 2000). DDR1a does not have this region but has a motif of Shc union (Playford et al., 1996). So DDR1a and DDR1b are able to transmit the signal inside the cell recruiting the adaptors proteins (Foehr et al., 2000), but still are unknown the following proteins in the cascade. It has been described in different studies that DDR1a and DDR1b have different biological functions (Ardeshna et al., 2000; Bhatt et al., 2000; Hacker et al., 1998; Vogel et al., 2001).

Citosomal region or intracellular: tyrosine kinase domain and C-terminus

The cytoplasmic region contains 438 aminoacids (438-911) and includes the kinase domain (Foehr et al., 2000; Playford et al., 1996). This domain is identical in a 39% to the kinase domains of neurotrophins (trk A/B/C) and shares some characteristics with these receptors (Koo et al., 2006).

The phosphorylation of the DDR receptors is very slow, at least 2 hours; this is one of the most important
characteristics of DDRs, which is not usual in the receptors tyrosine kinases (Ram et al., 2005; Shrivastava et al., 1998).

The C-terminus region is unusually short for a TKR and contains only 9 aminoacids (Ram et al., 2005).

**DDRs signalling**

DDR1 and DDR2 have 13 and 15 tyrosine kinase residues, respectively, in the cytoplasmic region that can be phosphorylated after collagen activation (Foeh et al., 2000; Playford et al., 1996). DDR1 signalling cascade differs with the cell type. In macrophages, phosphorylation occurs via Shc, TRAF6, p38 and NFκB (Matsuyama et al., 2003). In the mammary epithelial cells, the signalling cascade takes place via Stat 5, while in the tumor mammary cells the signal comes from another receptor: Frizzled (Dejmek et al., 2005).

Up to date, DDR2 signalling is rather unknown. Recent studies had revealed that DDR2 signalling requires the union of Shc A and Src (Ikeda et al., 2002).

**DDRs functions**

The unique ligand described of DDRs is the fibrillar collagen, a key component of the extracellular matrix. Therefore, the cellular functions of DDRs are directly related to the extracellular matrix. In vitro studies of different cell types derived from DDR1 and DDR2 deficient mice show that both receptors are important in the interaction between the cells and the extracellular matrix and are involved in: 1) Cellular adhesion and proliferation (Curat and Vogel 2002; Olaso et al., 2002; Vogel, 2002); 2) cell migration (Hou et al., 2001); and 3) extracellular matrix degradation via MMP activation (Hou et al., 2002; Olaso et al., 2002).

**DDRs role in development**

Although DDR1 and DDR2 deficient mice are viable, it is obvious that the expression of these genes is extremely important for the normal development (Labrador et al., 2001; Vogel et al., 2001).

The DDR1 deficiency produces problems in mammary gland formation, kidney and muscular development, directly related with cell proliferation and chemotaxis (Curat and Vogel 2002; Hou et al., 2002; Vogel et al., 2001). Regarding the DDR2 absence, the knock-out mice are dwarf and it is due to the decrease of chondrocytes proliferation capacity during long bones formation (Labrador et al., 2001).

**DDRs in liver cirrhosis**

The fibrotic stage is previous to the liver cirrhotic disease and it is characterized by the extracellular matrix remodel-ling (Friedman, 2003), MMP production (Olaso and Vidal-Vanaclocha, 2003), and fibrillar collagen accumulation (Tsukada et al., 2003). The transdifferentiation of hepatic stellate cells (HSCs) into myofibroblasts is a central event in the fibrogenic responses to hepatic injury induced by non-neoplastic (Friedman, 2003) and neoplastic processes (Amann et al., 2003; Jut et al., 2009; Matsusue et al., 2009). Major features of fibrogenic HSCs are the expression of myofibroblastic marker smooth muscle cell actin (SMA) and tyrosine kinase receptors such as PDGFR-β (Wong et al., 1994) and discoid domain receptor 2 (DDR2) (Olaso et al., 2001); the proliferation and migration into areas of tissue injury (Ikeda et al., 1999), the extracellular matrix production and remodelling (Tsukada et al., 2006), and the secretion of multiple soluble factors that regulate the migration and proliferation of other cell types including liver sinusoidal endothelium cells (LSECs) (Mendoza et al., 1998), parenchymal cell progenitors (Bhatia et al., 1999) and even cancer cells (Desmoulière et al., 2004; Mendoza et al., 1998; Olaso et al., 2003). It has been demonstrated that DDR2 signals for the HSC transdifferentiation process (Olaso et al., 2003). The lacking of DDR2 in the hepatic stellate cells reduce the fibrillar collagen and MMP production (Olaso et al., 2001), therefore the down-regulation of DDR2 reduces the fibrotic characteristics of HSC *in vitro* (Olaso et al., 2002). The critical role of the hepatic stellate cells transdifferentiation during liver fibrosis development and the specific activity of DDR2 in this process make the cell and the receptor good candidates as therapeutics targets for future therapies.

**DDRs in lung fibrosis**

Until now only DDR1 has been described in the lung fibrosis (Avivi-Green et al., 2006). The activation of the fibroblast due to external insults is the key event in the lung fibrosis. The presence of the DDR1 in these cells and the surrounding stroma has been described in different studies (Matsuyama et al., 2005, 2006a). In the case of the DDR1 knock-out mice, bleomycin-induced lung fibrosis developed slower than the wild types and it was directly related with less myofibroblast proliferation and migration capacity (Avivi-Green et al., 2006). About the surrounding stroma the DDR1 was localized in the bronchoalveolar lavage fluid and it was reported an important increase of MMP-9, IL-10 and MCP-1 related with an inflammatory microenvironment (Matsuyama et al., 2005). In the study of the DDR1 implication in the lung fibrosis it has been tested a kind of therapeutic approach using small interference RNA. Several siRNA were administrated to bleomycin-induced lung fibrotic mice and the fibrosis decreased in these animals compared with the wild types. The reduction of inflammatory cells, cytokines and collagen deposition were statistically significant (Matsuyama et al., 2006b).
DDRs in cancer disease

DDR1 has been described usually as a receptor expressed for several tumor cell types such as mammary, brain, lung or colon (Day et al., 2008; Park et al., 2007; Yan et al., 2010). This feature makes sense with the different signalling processes described by the DDR1 in the healthy tissue. The cell proliferation capacity (Olaso et al., 2002, 2003), migration ability (Olaso et al., 2001), and extracellular matrix degradation (Olaso et al., 1997, 2002), are essential characteristics of the cancer cells. The deregulation of these capabilities are tightly related with tumor progression and bad prognosis. For this reason it is reasonable to find an overexpression of DDR1 in several tumor cell types giving to the cancer cells their malignant characteristics.

In the case of DDR2 and cancer, most of the findings have been related with the tumor surrounding stroma (Olaso et al., 2001). The tumor metastasis capacity is not only related with the malignant characteristics of the tumor cells, also the tumor surrounding stroma is important for the metastasis development (Olaso and Vidal-Vanaclocha, 2003). This fact is the so called tumor microenvironment or seed and soil theory (Fidler, 2003). The tumor microenvironment theory says that the tissues hosting the tumor has to be special and specific to support the tumor and during the disease development this tissue suffers changes that produces a special inflammatory status helping the metastatic process (Mendoza et al., 2001). This process has been well described in the liver metastasis and the hepatic stellate cell transdifferentiation in myofibroblast phenotype is the pivotal activity (Friedman, 2003). DDR2 has been described as a receptor excreted in the healthy liver tissue but at the meantime DDR2 is the natural ligand, producing an interesting loop which produces more fibrillar collagen production which finally is the natural ligand, producing an interesting loop which appears frequently in chronic diseases. This is the case of cirrhotic, fibrotic and cancer disease, all of them chronic disease related with slow but constant signalling receptors that perpetuate the processes.

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