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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

DDR family

During the study of tyrosine kinase receptors in the tumor cell signalling it was described the presence of a new family of receptors, the DDRs.

The peculiarity of this family is the presence of a homology domain to discoidin I. Discodin I of *Dictyostelium discoideum* is a lectin implicated in the cellular morphology and cellular aggregation (Devine *et al*., 1982). Until now it has been described two members of the DDR family: DDR1 and DDR2 (Vogel, 1999). Both have fibrillar collagen type I and III as ligands, but they can also attach to the collagens type II and V (Shrivastava *et al*., 1998; Vogel *et al*., 1997). The triple helical configuration of the collagen is essential for receptor activation but the glycosilation of the collagen is only essential in the case of the DDR2 (Vogel *et al*., 1997). One of the most peculiar characteristics of DDR receptors is the slow phosphorilation that in the other hand persist in the time more than other tyrosine kinase receptors (Vogel *et al*., 1997).

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 mesenglial 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 metaloproteinases 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

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(Labrador *et al*., 2001). Also, skin fibroblast derived from DDR2 deficient mice proliferate at a slower rate than wild type ones, which may explain the observed deficiencies in the wound healing (Olaso *et al*., 2001, 2002).

Gen structure of DDRs

The ddr1 gene was cloned for the first time in 1993 through hybridization of a consensus sequence of tyrosine kinase domain of Tirosine 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 trae (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 juxtamenbrane and 5 for the catalytic domain. Compared to other tyrosine kinase receptors, the juxtamenbrane 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 1 90.0 c M. In humans it is composed by 19 exons and in mouse by 18.

Protein structure of DDRs

The DDRs are formed by different regions:

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 previous dimerization of the receptor (Letinger, 2003), and this is not the classical concept of TKR activation where the dimerization 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 juxtamenbrane region has 176 aminoacids, is rich in prolins 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 motiv, which is important for Shc binding (Curat *et al*., 2001; Foehr *et al*., 2000). DDR1a does not have this region but has a motiv 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).

Citosolic 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 (Foehr *et al*., 2000; Playford *et al*., 1996). DDR1 signalling cascade differs with the cell type. In macrophages, phosphorylation occurs via Shc, TRAF6, p38 and NFk-β (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: Frizzleed (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 remodelling (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; Ju *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 discoidin 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 transdifferntiation 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 downregulation 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 this 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 this 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 metastatis 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*., 1998). This process has been well described in the liver metastasis and the hepatic stellate cell transdiferentiation in myofribroblast phenotype is the pivotal activity (Friedman, 2003; Olaso *et al*., 1997). At the same time the role of the DDR2 has been described in this HSC activation process and therefore the relation of DDR2 with the tumor microenvironment and the hosting tissue support to metastatic process is direct (Friedman, 2003).

But recently DDR2 also has been described in melanoma cell lines (Badiola *et al*., 2011). *In vitro* experiments described that downregulation of the DDR2 expression in the melanoma cell lines reduces their proliferation and migration capacity and *in vivo* studies show a considerable reduction of the metastatic capacity when DDR2 expression was partially silenced.

On the other hand it is important to consider the distinctive characteristics of DDRs respect to other TKRs. The low phosphorylation and the feed-back capacities. The phosphrolytaion of the receptors is slow compared with other TKRs but at the meantime the phosporylation 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 chirrotic, fibrotic and cancer disease, all of them chronic disease related with slow but constant signalling receptors that perpetuate the processes.

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