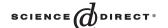


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Review

Sensing extracellular matrix: An update on discoidin domain receptor function

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Abstract

Discoidin Domain Receptors (DDRs) have recently emerged as non-integrin-type receptors for collagen. The two mammalian gene products Discoidin Domain Receptor 1 and -2 constitute a subfamily of tyrosine kinase receptors that are selectively expressed in a number of different cell types and organs. Upon collagen activation, DDRs regulate cell adhesion, proliferation and extracellular matrix remodeling. Here we review the various signaling pathways and cellular responses evoked by activated DDRs. Additionally, we give an overview of the more recent advances in understanding the role of DDRs in various human diseases, in particular during tumor progression, atherosclerosis, inflammation and tissue fibrosis. Furthermore, we discuss potential roles of genes homologous to mammalian DDRs identified in flies, worms and sponges. We show that the structural organization of these DDR-related genes is highly conserved throughout evolution suggesting that invertebrate DDRs may also function as receptors for collagen. By highlighting current questions about these unusual collagen receptors, we hope to attract new research on DDRs from a variety of different fields.

Keywords: Extracellular matrix; Collagen; Tyrosine kinase; Discoidin domain; Receptor signaling; Molecular evolution

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1. Introduction

Living cells must integrate a myriad of extracellular stimuli into highly cohesive responses. To manage this wealth of information, a diverse array of specialized cell surface receptors exists that binds extrinsic factors such as mitogens, differentiation factors, cell membrane-bound molecules or extracellular matrix (ECM) proteins, and then transmit signals through the plasma membrane. Many of these receptors belong to the family of receptor tyrosine kinases (RTKs) characterized by an extracellular ligand binding domain, a single transmembrane domain and a catalytic tyrosine kinase domain. RTKs have been grouped into 18 subfamilies according to the domain structure of their extracellular region, which defines ligand specificity [1]. This review focuses on one subfamily of RTKs, the Discoidin Domain Receptors (DDRs). Two members of this subfamily are present in the human genome, DDR1 and DDR2. DDRs are unique due to their ligand-specificity and remarkable conservation throughout evolution.

1.1. Being different — DDRs are a variation of the classical tyrosine kinase receptors

Unlike most other RTKs, DDRs are not activated by soluble growth factors. Instead, various types of collagen act as ligands for DDRs. DDR1 is activated by all collagens tested so far, including collagens type I to type VI and type VIII, while DDR2 is only activated by fibrillar collagens, in particular collagens type I and type III [2,3]. DDRs are activated only when collagen is in its native, triple-helical form, as heat-denatured collagen (gelatin), which lacks triple-helical structure, fails to induce kinase activity. While most other RTKs are fully activated in minutes, maximal activation of DDRs occurs several hours after the initial stimulation with collagen [2]. Some attempts have been made to further define the molecular interaction between collagen and DDRs, but the precise location of the DDR-binding site within triple-helical collagen is yet unknown. Recent work however suggested the second quarter of type II collagen has been as a possible binding site for DDR2 [4,5].

Four integrin receptors, formed between the $\beta 1$ subunit and the $\alpha 1, \alpha 2, \alpha 10$ or $\alpha 11$ subunit, also act as functional collagen receptors, but do not require DDRs as co-receptors [6]. Conversely, binding of collagen to integrins results in non-DDR-dependent tyrosine phosphorylation events, which are mainly driven by integrin-associated kinases of the Src- and Fak-family. An important and well-described outcome of integrin activation is the alteration in cytoskeletal tension and cell migration, which is mediated by the actomyosin network. In contrast to the integrins, a potential role of DDRs in transmitting these kinds of mechanical stimuli within or between cells has not been explored.

Structurally, DDRs are distinguished from other RTKs by a discoidin domain, an approximately 160 amino acid long homology region first identified in the protein discoidin I from the slime mold *Dictyostelium discoideum*, where it functions as galactose-binding lectin [7–9]. Aside from DDRs, the discoidin I-homology repeat is also present in more than a dozen other mammalian transmembrane as well as secreted proteins. Uti-

lizing the crystal structures of the discoidin domains found in the coagulation factors V and VIII, molecular models of the domains in DDR1 and DDR2 were generated [10,11]. Hallmark of these models is a central eight-stranded beta-barrel, which is stabilized by two intramolecular disulfide bridges, and four finger-like loops protruding from one side of the beta-barrel. The position of these loops is well conserved between discoidin domains of DDRs, blood clotting factors V and VIII or neuropilin [12]. Work with a recombinant preparation of the DDR1 discoidin domain led to the identification of loops 1 and 3 being essential for collagen binding and receptor activation [11]. However, one will have to await a detailed structural analysis of DDRs to draw more definitive conclusions on the architecture of the ligand-binding pocket.

In several cell lines and tissues, DDR1 is partially processed into a 62 kDa membrane-anchored beta-subunit and a 54 kDa soluble extracellular domain-containing alpha-subunit [13]. This process, also termed shedding, is significantly enhanced upon DDR1 activation. Proteases belonging to the ADAM or MT-MMP family could potentially be responsible for DDR1 shedding, since they have been pinpointed as sheddases for a number of other receptors involved in cell-adhesion, including Eph receptors, selectins and the heparin-binding epidermal growth factor [14,15]. In near future, more experimental work will hopefully "shed" better light on the mechanism of DDR1 processing.

Compared to other RTKs, the juxtamembrane regions of DDR1 and DDR2 are much longer (176 and 147 amino acids, respectively). As observed for members of the platelet derived growth factor receptor or Eph receptor subfamilies, we speculate that the juxtamembrane region of DDRs also has an autoinhibitory function [16]. For Eph receptors, it was found that sequences within the juxtamembrane region block the ATP binding site in the kinase domain and, upon ligand binding, need to be displaced prior to activation of the catalytic function. Potentially, the protracted kinetics of DDR activation are the result of a similar rate-limiting structural re-arrangement in the juxtamembrane region that is necessary to overcome an intrinsic auto-inhibition.

1.2. The complexities of DDR1 isoforms

Thus far, five isoforms of DDR1 have been identified, all of which are generated by alternative splicing in the cytoplasmic region [17]. The longest DDR1 transcript encodes the c-isoform with 919 amino acids. The a- and b-receptor isoforms lack 37 or 6 amino acids in the juxtamembrane or kinase domain respectively [9]. DDR1d and DDR1e are truncated variants that lack either the entire kinase region or parts of the juxtamembrane region and the ATP binding site [17]. In contrast, no isoforms have been identified for DDR2 yet.

The relative expression ratios and the post-translational modifications of the DDR1 a- and b-isoforms appear to be controlled by complex regulatory mechanisms. The DDR1b protein is the predominant isoform expressed during embryogenesis, whereas the a-isoform is commonly found in several human mammary carcinoma cell lines [18]. Furthermore,

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