Discoidin domain receptors: multitaskers for physiological and pathological processes

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Discoidin domain receptors 1 and 2 (DDR1 and DDR2) are key cellular receptors for cell-matrix interactions that belong to the family of receptor tyrosine kinases. Both DDRs interact with various collagens, with each DDR exhibiting specificity towards certain collagen types [1]. Like matrix-interacting integrins, the DDRs participate in cell adhesion and mechanosensing processes. Additionally, the DDRs play a role in cell-cell adhesion. Consequently, the DDRs can be used by cells to sense and control their microenvironments. In contrast to typical receptor tyrosine kinases that react quickly to ligand binding, the DDRs exhibit an intrinsic kinase activity with slow and prolonged activation [2].

The DDRs are promising therapeutic targets for a wide variety of human diseases. However, we are far from fully understanding their physiological roles in development or adult tissues. Their functions during various pathologies are complex, with wide-ranging and often opposing roles in cell proliferation, invasion, fibrosis or inflammation.

In this special issue several reviews and original articles give a synopsis of DDR function in various biological contexts. The commentary by Cario-André focuses on the roles of the DDRs in skin, where there is a complex situation with differential DDR expression in the dermis and epidermis. This expression pattern is mirrored by differential DDR expression in the dermis and epidermis. Expression of DDR1 and DDR2 is important for melanocyte adhesion, whereas DDR2 regulates melanoma invasion (2017CAM0057R1, in press). DDR1 is known to regulate kidney architecture and has been widely studied in renal diseases. Dorison and Chantziantoniou highlight the involvement of DDR1 in the proinflammatory and pro-fibrotic processes of chronic kidney disease [3]. In addition to kidney, DDR1 has emerged as a possible biomarker and therapeutic target for fibrotic disorders in heart, liver, lung and perivascular tissues. Indeed, DDR1 clusters as a mechanoreceptor and using myosin IIA can modulate contraction of collagen fibrils and consequently tissue stiffness [4]. Interestingly, the organization and the structure of collagen can promote specific and variable responses through DDRs. This point is highlighted by the impact of collagen aging on DDR1-mediated cell proliferation and apoptosis in non-invasive breast carcinoma cells [5].

Another important question raised by some authors concerns the regulation of DDR expression and the cross-talk of the DDRs with other signalling pathways. On the one hand, various growth factors, including VEGF, TGF-β and IGF, are involved in regulating the expression of DDR1 or DDR2 [6–8]. On the other hand, DDR signaling can also intersect directly with the signalling pathway of other receptor tyrosine kinases. In this regard, Belfiore et al. established that DDR1 interacts with IGF-1R and modulates its signaling in breast cancer [9].

The DDRs are well-established players that contribute to tumor cell invasion and metastasis formation. In his review Itoh describes how the DDRs can modulate cell migration and invasion, with a particular focus on their roles in matrix metalloproteinase expression and activity. Itoh further highlights that DDR-mediated regulation of cell invasion extends beyond a function in cancer to other human diseases such as osteoarthritis and rheumatoid arthritis [10]. In another commentary, Chakraborty and Gadiya produce an update on data regarding DDR expression, mutations and signaling in cancer (KCAM-2018-0015, in press). The DDRs have also been implicated in chemoresistance. In this special issue, Santamaria and colleagues discuss the role of DDR1 in pro-survival functions in the development of cancer resistance to chemotherapeutics [11]. Along the same lines, Henriet et al. highlight the involvement of the DDRs in several and
specific hallmarks of cancer. In accordance with other manuscripts of this issue, they describe the role of DDR1 and DDR2 in proliferation, migration, angiogenesis invasion and metastasis [12].

While it has been thought that DDR expression was mutually exclusive, Croissant et al. demonstrate that DDR1 and DDR2 can be expressed in the same cell and physically interact with one another. The co-expression of DDR1 with DDR2 modulates cell migration [13]. This observation is supported by the known cellular localizations of DDR1 and DDR2, including to cell-cell junctions and also along type I collagen fibrils [12]. Further experimental work is required to evaluate the impact of DDR1 and DDR2 co-overexpression in cancer.

Several articles of this special issue address the point that the DDRs should be considered as targets in various diseases such as fibrosis or cancer. Currently, DDRs are considered as a promising target in cancer therapy, due to the fact that emerging evidence suggests crucial roles for the DDRs in tumor progression and metastasis formation in various solid tumors. Some inhibitors are known to efficiently block DDR kinase activity such as dasatinib or nilotinib. Currently, more selective DDRs inhibitors are developed or under development (refs). It is hoped that targeting DDRs will result in therapeutic benefits.

Overall, the articles in this special issue clearly demonstrate the complex and multiple roles the DDRs play in crucial physiological and pathological processes. However, the DDRs are still underestimated and remain an under-researched area. Fortunately, the number of publications is increasing, but there is still much to discover about the fundamental aspects of DDR biology.

Finally, we would like to thank the leading experts in this field who kindly contributed to or peer-reviewed this special issue.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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