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AUTHOR'S VIEWS

DDR1 inhibition as a new therapeutic strategy for colorectal cancer

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ABSTRACT

The clinical management of metastatic colorectal cancer (mCRC) is still a major challenge. Recently, we discovered that nilotinib, an approved treatment for chronic myeloid leukaemia, inhibits invasive and metastatic properties of CRC cells by targeting the kinase activity of receptor for collagens DDR1 (Discoïdin Domain Receptor tyrosine kinase 1), suggesting that nilotinib could be an effective strategy to treat mCRC.

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Colorectal cancer (CRC) is one of the leading causes of mortality and morbidity in the world. The current clinical management of CRC involves surgical removal of the localized tumour, often associated with neoadjuvant radiotherapy or adjuvant chemotherapy. However, tumour recurrence occurs in about one third of patients, resulting in poor prognosis with 5-year survival rates ranging from 10 to 30%. Therapeutic failure is usually associated with metastatic spread, when cancer cells escape from the primary tumour to disseminate and establish secondary tumours in distant organs. Metastatic cell behaviour is characterized by invasive properties and tumour-initiating capacities, which are under the control of the tumour microenvironment.[1] Therefore, targeting this metastatic process may be of obvious therapeutic interest in advanced CRC.

Discoïdin Domain Receptor tyrosine kinase 1 (DDR1) is a tyrosine kinase receptor for collagens, ones of the major components of the extracellular matrix (ECM).[1,2] DDR1 functions as a central ECM microenvironment sensor to regulate cell adhesion and to promote tumour cell invasion and cancer stem cell survival in a collagen rich environment.[3,4] Curiously, the role of DDR1 kinase activity in cancer is poorly documented and its kinase activity seems to be dispensable for several DDR1 reported functions such as collective cell migration of squamous cell carcinoma, cell invasion and metastatic reactivation in breast cancer.[5] One notable exception is the lung cancer where KRAS (Kirsten Rat Sarcoma viral onocogen homolog) mutations induce DDR1 expression and sustains Notch oncogenic signalling and tumorigenesis.[6]

In our recent study published in EMBO Molecular Medicine,[7] we report an additional important DDR1 kinase-dependent function in invasive and metastatic abilities of CRC cells. First, we discovered that the tyrosine kinase inhibitor nilotinib, which targets BCR-ABL (Breakpoint Cluster Region-Abelson fusion oncogene) and is currently used to treat patients with imatinib-resistant chronic myeloid leukaemia,[8] strongly inhibits the invasive properties of CRC cells in vitro and their metastatic abilities in intrasplenic nude mice xenograft models. As ABL (Abelson Protein Kinase) is not deregulated in CRC cells, we speculated the involvement of an alternative target. Interestingly, even if very few nilotinib off-targets have been originally described, proteomics profiling identified DDR1 as its highest affinity target.[9] Based on this data, we hypothesized that DDR1 could be the main target of nilotinib in CRC cells. Consistently, our results establish a central role of DDR1 kinase activity in this malignant process, as indicated by the loss of invasive properties in DDR1-depleted cells or cells expressing a DDR1 kinase-dead mutant. We also showed that DDR1 promotes metastatic formation in nude mice. We next confirmed that DDR1 is the main target of this nilotinib anti-tumour activity using CRC cells expressing a nilotinib-resistant form of DDR1. Interestingly, DDR1 pharmacological inhibition by nilotinib inhibits the invasive and metastatic behaviour of CRC cells through a RAS-independent mechanism, which could be of major therapeutic interest in CRC, as only patients with wild-type RAS tumours benefit from anti-EGFR (Epidermal Growth Factor Receptor) targeted therapies. By shot-gun phosphoproteomics, we identified BCR (Breakpoint Cluster Region) as a critical DDR1 substrate involved in the maintenance of the β-catenin transcriptional activity, which is necessary for tumour cell invasion (Fig. 1). Indeed, we showed that, by phosphorylating BCR on Tyr177, DDR1 disrupts a negative regulatory loop on β-catenin signalling to sustain its oncogenic activity. In agreement, DDR1 activity induces expression of β-catenin target genes that are important for cell motility and CRC stem cell properties, such as *JUN*, *FOSL1*, *CD44*, *MYC*, *CCND1*, *LGR5* and *AXIN2*[7]. Consistently with this idea, DDR1 also promotes β-catenin nuclear activity during liver metastatic development, which can be inhibited by nilotinib treatment. Due to

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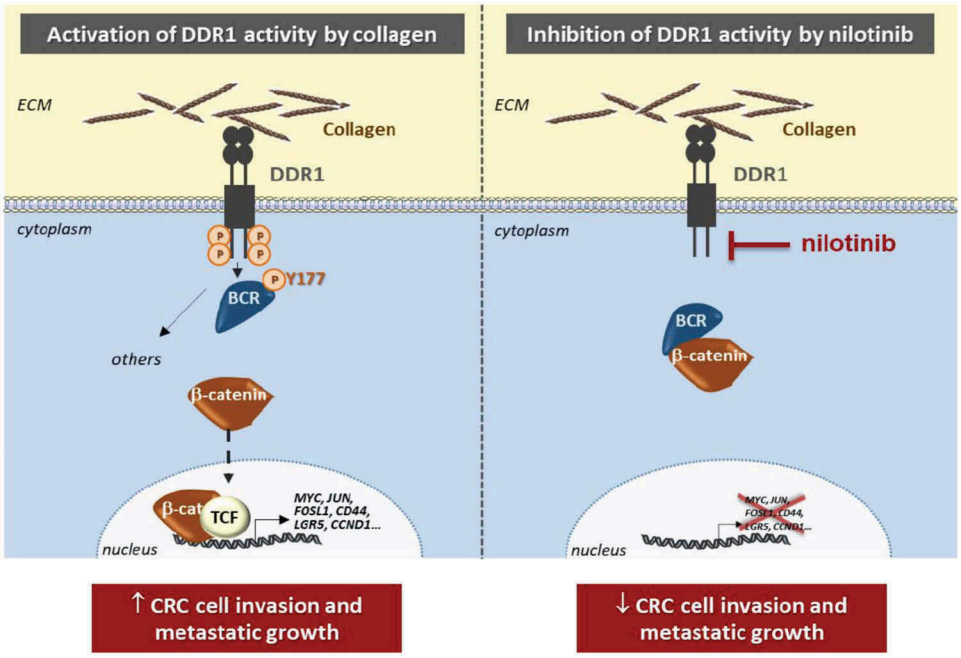

Figure 1. Inhibition of DDR1-BCR signaling by nilotinib. Collagens from the extracellular matrix (ECM) microenvironment of colorectal cancer (CRC) cells induce the kinase activity of DDR1 (Discoïdin Domain Receptor tyrosine kinase 1), which phosphorylates its substrate BCR (Breakpoint Cluster Region) on the tyrosine 177 (Y177), subsequently disrupting BCR/β-catenin interaction. This signaling cascade results in an increased β-catenin/TCF (T-Cell Factor) nuclear activity leading to the expression of critical target genes (including *MYC, JUN, FOSL1, CD44, LGR5, CCND1*) necessary for cell invasion and metastatic development (left panel). Inhibition of DDR1 kinase activity with nilotinib decreases CRC cell invasion and metastasis by reducing this β-catenin pathway (right panel).

the major role of the Wnt/β-catenin pathway in CRC, we thus proposed that DDR1 acts by supporting β-catenin oncogenic activity upon adhesion to collagens present in the tumour microenvironment to sustain tumour cell migration, survival and renewal.

Clinical relevance of our findings was further supported by showing that a high DDR1 expression level is an independent marker of poor prognosis in stage IV patients and that its relative kinase activity is dramatically increased in CRC metastatic nodules from a cohort of patients, when compared to non-transformed tissue or primary tumours of the same patients. Additionally, we showed that nilotinib inhibits the DDR1-mediated invasive and metastatic potential of patient-derived cell lines originating from metastatic tumours or from circulating CRC cells.[10] Finally, nilotinib also displays anti-tumour activity in mice that have already developed DDR1-dependent metastatic nodules, revealing an additional important role of DDR1 activity in metastatic growth.[7] These observations are consistent with previous reports showing that DDR1 is pro-invasive in various cell lines derived from tumours of epithelial origin and that DDR1 has a metastatic function in lung and breast cancer,[5,6] highlighting a conserved function of DDR1 in invasive tumours. Although some DDR1-kinase independent functions may be expected, we established here the central role of the kinase activity of DDR1 in metastasis.

In conclusion, our findings indicate that targeting tumour signalling emanated from the microenvironment through inhibition of DDR1 activity could be an effective RAS-independent therapeutic strategy to treat advanced CRC and suggest that repositioning nilotinib in metastatic CRC may be of therapeutic value.

Disclosure of potential conflict of interest

No potential conflict of interest was disclosed.

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