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. Therefore, targeting this metastatic process may be of obvious therapeutic interest in advanced CRC.

Discoidin Domain Receptor tyrosine kinase 1 (DDR1) is a tyrosine kinase receptor for collagens, one of the major components of the extracellular matrix (ECM). 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. 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. One notable exception is the lung cancer where KRAS (Kirsten Rat Sarcoma viral oncogene homolog) mutations induce DDR1 expression and sustains Notch oncogenic signalling and tumorigenesis.

In our recent study published in EMBO Molecular Medicine, 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, 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 hypothesized that DDR1 could be the main target of nilotinib inhibition by nilotinib inhibits the invasive and metastatic behaviour of CRC cells through a RAS-independent mechanism, which could be major therapeutic interest in CRC, as only patients with wild-type RAS tumours benefit from anti-EGFR (Epidermal Growth Factor Receptor) targeted therapies. By shotgun 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. Consistently with this idea, DDR1 also promotes β-catenin nuclear activity during liver metastatic development, which can be inhibited by nilotinib treatment. Due to
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. Finally, nilotinib also displays antitumour activity in mice that have already developed DDR1-dependent metastatic nodules, revealing an additional important role of DDR1 activity in metastatic growth.

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
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