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A novel germline mutation of PDGFR-β might be associated with clinical response of colorectal cancer to regorafenib.

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We report an extraordinary response to regorafenib in a patient with metastatic adenocarcinoma of the rectum. In order to identify the molecular target of this response, we analysed 409 cancer genes by next generation sequencing of the genomic DNA (patient tumor and blood) and discovered a germline mutation of the PDGFR-β gene, a target of regorafenib. The patient (male, Caucasian) was diagnosed with rectal cancer at the age of 37 years; the initial stage was pT3pN0cM0. The patient underwent initially a rectal resection and adjuvant chemotherapy. Seven years later, recurrence of disease with metastases was diagnosed. Molecular analysis of the tumor demonstrated a KRAS wildtype genotype. The patient underwent multiple systemic treatments over five years. At this time the patient became symptomatic with pain and cough due to bone and lung metastases (Fig.1a). Treatment with regorafenib was initiated. After eight weeks, a PET/CT scan showed a partial morphological and metabolic response (Fig. 1b) according to RECIST criteria. After 9 months from beginning of this therapy the patient is still in partial remission with significant improvement of the symptoms (Fig. 1c). Regorafenib inhibits the angiogenic and stromal receptor tyrosine kinases (RTKs), vascular endothelial growth factors receptors (VEGFRs), tyrosine kinase endothelial 2 (TIE2) and platelet derived growth factor receptor β (PDGFR-β). In colorectal cancer patients, objective responses to regorafenib have been rarely observed (1% response rate [1]). As our patient showed a response lasting over 9 months, we analysed the patient’s tumor by next generation sequencing (NGS) using targeted amplification with the AmpliSeq [2] Comprehensive Cancer panel (CCP; Ion Torrent, Life Technologies) which includes all exons of 409 cancer genes; the amplified regions were sequenced according to [3]. Alignment, variant calling, and filtering were done with Ion Reporter v4.0 (Life Technologies) and are summarized in supplementary Table 1 and 2. We detected a non-synonymous point mutation of PDGFR-β at codon 6 (p.A6V) which was confirmed by Sanger sequencing (Fig. 2a). This mutation has already been described in the COSMIC database (ID=1435169) as a unique case out of 367 colon carcinomas investigated. As this represents a rare mutation, we sequenced this region in the genomic DNA derived from the patient’s peripheral blood mononuclear cells (PBMCs) and detected the same strong heterozygous signal, demonstrating this to be a germline mutation (Fig. 2b). Moreover, we could exclude the presence of this mutation in the genomic DNA derived from tumor samples of four patients affected by metastatic colorectal cancer not responding to regorafenib (Fig. 2c). A strong and homogenous expression of PDGFR-β could be detected in the patient’s tumor compared to the non-responder patients (Supplementary Fig. 1). PDGF and their receptors (PDGFR-α, PDGFR-β and PDGFR-αβ) play a critical role in cancer development [4, 5]. Mutations involving up-regulation of PDGF and/or PDGFR have been documented in a number of solid tumors and hematological malignancies. In colon cancer, previous reports have shown sensitivity of a cell line with mutation (p.T681I) of PDGFR-β, to sorafenib [6] and a recent case report described another germline
mutation in exon 19 of PDGFR-β [7] associated with increased pathway activation and survival. To date, mutations of PDGFR-β have not been correlated to response to regorafenib, neither in cell lines nor in patients. Here we describe for the first time the germline mutation c.17C>T (NM_002609.3) of PDGFR-β, a target of regorafenib and hypothesize that this mutation, in the signal peptide of PDGFR-β, might have an oncogenic driver potential [8]. Although objective responders to regorafenib are rare, it would be of major interest to confirm this result in a larger group of patients to define if PDGFR-β is a predictive marker to this treatment.

The authors declare no conflicts of interest.

**Legend to Figures and tables**

**Figure 1.** PET-CT scans at baseline (a), after 8 weeks of treatment (b), after 5 months of treatment (c).

**Figure 2: Sanger sequencing of PDGFR-β.** a) To verify the variant in PDGFR-β which was detected by NGS in the responder to regorafenib, the same DNA derived from tumor tissue as used for NGS was amplified for the region of interest and sequenced by Sanger sequencing. The variant p.A6V was successfully verified. b) To investigate whether the verified mutation in PDGFR-β is tumor specific, DNA was isolated from PBMCs (blood) from the responder to regorafenib and sequenced by Sanger sequencing. The variant p.A6V was detected in PBMCs as well and thus defined as germline mutation. c) To analyse whether the germline mutation p.A6V in PDGFR-β may be a private mutation in the responder to regorafenib, tumor samples of four additional colon carcinoma patients which did not respond to regorafenib treatment were sequenced for the specific mutation in PDGFR-β. None of the non-responders to regorafenib exhibited the mutation p.A6V.
Figure 1
Figure 2

Patient # DNA derived from:

- #1 Blood (FAML-5)
- #2 Primary adenocarcinoma of the colon
- #3 Primary adenocarcinoma of the sigma (pT3, pN1, M1)
- #4 Lung metastases of an adenocarcinoma
- #5 Liver metastases of an adenocarcinoma

Non-responders
Responder
Regretted treatment