Serum marker for diagnosis, prognosis and therapy monitoring of colorectal carcinoma

Integrin αvβ6 has been identified as a serum marker for the diagnosis and prognosis of colorectal carcinoma. The level of integrin αvβ6 in the serum correlates with the presence of metastasis and chance of surviving the disease. It is furthermore a marker for monitoring response to therapy.

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Invention
Serum samples from healthy control patients (n=19) and patients with colorectal carcinoma (n=329) were analysed by ELISA. As shown in Fig. 1 a serum concentration of integrin beta 6 above 2 ng/ml means 100% metastatic disease. It furthermore means worse survival (Fig. 2). Integrin beta 6 serum level is associated with a metastatic status of CRC in contrast to the level of CEA.

Our findings also demonstrate that integrin beta 6 can be used as a marker for therapy response and tumor surveillance (Fig. 3). In a prospective cohort of CRC patients, almost no detectable ITGB6 serum levels were observed in patients without lymph node or organ metastasis (blue dots). The four patients with lymph node metastasis (LN+) (stars) revealed an ITGB6 serum level of 0.25–1.94 ng/mL pre-surgery, which dropped to 0.00–0.07 ng/mL post-surgery. We observed an increase of ITGB6 to 1.40 ng/mL in one patient (red star), who was diagnosed with liver metastasis at a second follow-up visit (80 weeks after surgery). In four patients with liver metastases (triangles), pre-surgery ITGB6-levels were between 0.79–1.98 ng/mL. All of those patients revealed lower levels of ITGB6 during follow-up visits after surgery (0.06–1.21 ng/mL). One of those patients underwent resection of the primary tumor and the liver metastasis, in which ITGB6-levels declined completely after surgery (brown triangle). Two patients showed a clear decrease in ITGB6-levels after resection of the primary tumor and remained stable during adjuvant chemotherapy for the remaining liver metastases. The fourth patient (red triangle) showed a complete decline of ITGB6 serum level after resection of the primary tumor. However, a significant increase during follow-up visit was observed that was diagnosed with a progression of the liver metastasis. While we detected a direct correlation of tumor resection to a decrease of ITGB6 serum levels, no such correlation was found for serum CEA-levels in our patients (Fig. 4). These observations suggest that ITGB6 not only serves as a serum biomarker for diagnosis of mCRC and CRC prognosis, but also as a marker for tumor surveillance, relapse and treatment response. Regarding all of those aspects, ITGB6 serum levels seem to be a superior marker compared to the routinely used CEA.

Fields of Use
The invention can be used for the diagnosis of metastasizing colorectal carcinoma, prognosis of colorectal carcinoma and also for monitoring response to therapy/occurrence of relapses.
**Fig. 1**

$\beta_6$-integrin serum level $\geq$ 2.0 ng/ml indicates metastatic CRC

**Fig. 2**

Elevated $\beta_6$-integrin Serum Level Indicates Poor Survival

- HR 2.524 (95% CI: 1.463-4.355) for $\beta_6$-integrin serum level $\geq$ 0.10 ng/ml
- HR 5.189 (95% CI: 2.801-9.612) for $\beta_6$-integrin serum level $\geq$ 2.00 ng/ml
Fig. 3

β₆-integrin Serum Level as a marker for treatment response, surveillance and tumor relapse

![Graph showing β₆-integrin Serum Level with markers for different states](image)

- Tumor free after surgery
- Liver metastasis in situ after colon surgery, under chemotherapy
- Liver metastasis in situ after colon surgery, progression at follow-up 1
- New liver metastasis detected

Fig. 4

β₆-integrin Serum Level is better than CEA for detecting treatment response and tumour recurrence

![Graph showing comparison between β₆-integrin Serum Level and CEA levels with markers for different states](image)

- Tumour free after surgery
- Liver metastasis in situ after colon surgery, under chemotherapy
- Liver metastasis in situ after colon surgery, progression at follow-up 1
- New liver metastasis detected