

# New therapeutic target for a type of colorectal cancer with poor prognosis has been identified

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Researchers at the Institut Hospital del Mar d'Investigacions Mèdiques (IMIM) have identified a new way of treating colorectal cancer. In the study published in the journal *Science Signaling*, the team led by Lluís Espinosa, investigator of IMIM's research group into stem cells and cancer, have shown that inhibition of endosomal activity is a potential therapeutic strategy for the treatment of cancers with the BRAF mutated gene. This discovery is an important step in the personalisation of the treatment of colorectal cancer, as the presence of this mutation is associated with an increased resistance compared to standard therapies. Researchers from IDIBELL - the Catalan Institute of Oncology also participated.

Colorectal [cancer](#) (CRC) is the second leading cause of [cancer death](#) in the Western world. Tumours which carry mutations in KRAS genes (40% of CCR) or BRAF genes (between 5 and 15% of these types of cancers) are ineffectively treated and have poor prognosis. "KRAS inhibitor medications are extremely toxic and the use of BRAF inhibitors is limited because tolerance to them can be quickly acquired. This is why identification of new therapeutic targets is vital to improving [treatment](#)," explains Dr. Espinosa.

For this project, researchers studied samples from 98 [colorectal cancer](#) patients with different mutations in KRAS and BRAF genes. The results show that although mutant KRAS and BRAF proteins activate similar

pathways, they act differently on elements of the NF- $\kappa$ B pathway (only KRAS activates NF- $\kappa$ B), one of the most important pathways in the regulation of innate and acquired immunity. Partly related to its function as a regulator of the immune response, the NF- $\kappa$ B pathway is also a key regulator of cancer progression. Therefore, the blockage of this pathway is one of the most commonly suggested strategies for the treatment of this disease. In this context, "Identifying differences in the behaviour of KRAS and BRAF on NF- $\kappa$ B elements is an important step in the personalisation of treatment based on inhibition and in designing specific strategies for each type of cancer. Our results indicate that inhibitors of NF- $\kappa$ B would have no effect on BRAF mutated tumours, unlike KRAS mutated tumours", says Dr. Lluís Espinosa.

In addition, the results of the study have initiated a new therapeutic strategy based on the inhibition of the P45- $\text{IKK}\alpha$  enzyme, a protein that is essential in the case of BRAF mutated tumours, for tumour progression. This enzyme (P45- $\text{IKK}\alpha$ ) is generated in the endosomes, a cellular organelle that transports material which has just been added to the cells and which needs a specific acidic environment for optimal performance. The experiments have shown that the inhibition of endosomal acidification prevents the activation of P45- $\text{IKK}\alpha$  and specifically inhibits the growth of cancer cells with mutant BRAF, both in vitro and in vivo. "We show that these endosomal inhibitors, currently used in, for example, the prevention and treatment of malaria can be used to prevent metastasis of colorectal cancer, without increasing the toxicity of standard treatments. In fact, we found the inhibition of acidification of endosomes enhances the effect of conventional chemotherapy in mice," says Dr. Lluís Espinosa.

Although these results are an important step forward in understanding the mechanisms of tumour progression, more research is needed before this treatment can be applied to clinical practice. The current focus of the research team is to identify new endosomal function inhibitors that

are more efficient and more specifically focused on the P45-IKK $\alpha$  enzyme.

**More information:** "BRAF-induced tumorigénesis is IKKalpha dependiente but NF-kB independiente" (BRAF induced tumorigenesis is IKKalpha NF-kB dependent but independent"). Polo Margalef, Carlota Colomer, Alberto Villanueva, Clara Montagut, Mar Iglesias, Beatriz Bellosillo, Ramón Salazar, María Martínez-Iniesta, Manolis Pasparakis, Anna Bigas, and Lluís Espinosa. *Science Signaling*.

Provided by Hospital del Mar Research Institute

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