Topic: From bench to bedside: new perspectives for precision medicine

MECHANISMS OF ACQUIRED RESISTANCE TO CETUXIMAB: ROLE OF INTERLEUKIN 1

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Abstract

Cetuximab (CX) is a monoclonal antibody targeting the Epidermal Growth Factor Receptor (EGFR), which is commonly utilized to treat patients with metastatic colorectal cancer (mCRC). Unfortunately, clinicians often observe a residual disease, with a population of cells surviving the treatment and eventually enabling CX resistance. Our previous studies, performed with a cohort of 150 CRC xenopatients, associated poor response to CX with increased abundance of a set of inflammatory cytokines, including IL1A, B and IL8. Stemming from these observations, our working hypothesis assumes that, resistance to CX is acquired, in a subset of CRC patients, through cell plasticity and consequent rewiring of signalling networks, which confer to tumors dependency on the IL1 pathway. In order to assess the effect of IL1 activity, we employed a colon cancer model unresponsive to cetuximab, as previously characterized in our laboratory. To inhibit activation of the IL1 pathway we used anakinra, an IL1-receptor antagonist and parthenolide, which modulates the activity of NF-kB, the transcription factor involved in the feed-forward loop of inflammation mediators. Furthermore, we employed a recombinant decoy (IL1R-Fc), namely a soluble protein combining the human immunoglobulin Fc portion linked to the extracellular region of IL1-receptor, with the ability to sequester IL1 directly from the medium. We generated stable clones of CX-resistant cells expressing IL1R-Fc. Our preliminary results show that inhibition of IL1R leads to a proliferation decrease of colorectal cancer cells. These findings support the hypothesis of a compensatory activation of the IL1-receptor pathway in cetuximab-resistant CRC cells. Hence, inhibiting IL1 signalling might represent a new therapeutic strategy suitable for patients who acquired refractoriness to monoclonal antibody therapy.

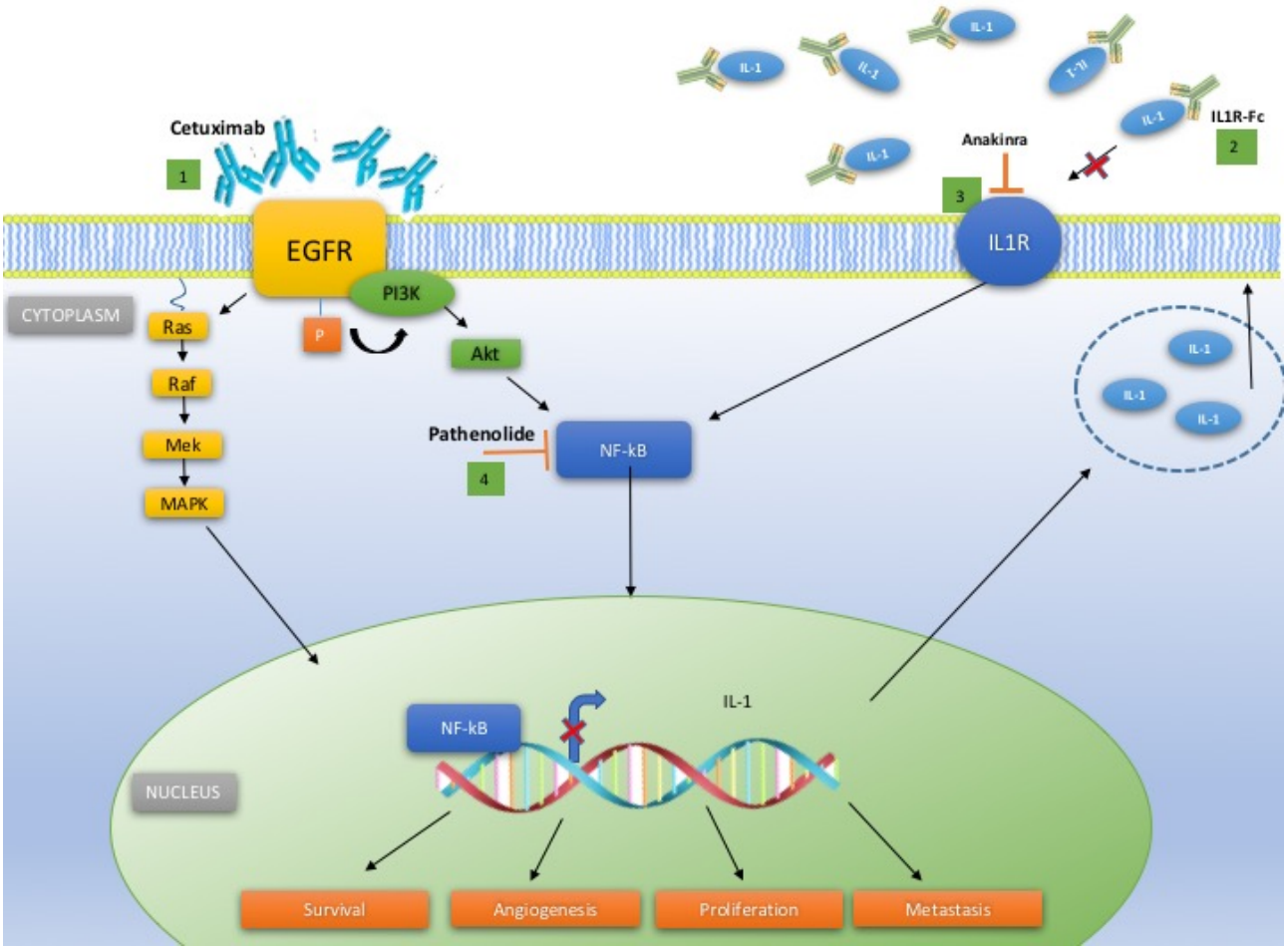

Figure 1. : Inhibition of IL1R pathway. 1: Inhibition of EGFR with Cetuximab. 2: IL1R-Fc prevent IL-1 binding. 3: Anakinra, bind and blocks IL1R. 4: parthenolide prevents translocation of NF-kB to the nucleus blocking IL-1 transcription