CLIC1: A MARKER OF UNCERTAIN DIAGNOSTIC VALUE AND UNKNOWN AS THERAPEUTIC TARGET

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INTRODUCTION

Chloride intracellular channel 1 (CLIC1) is a member of the human CLIC family, a group of substances that regulate chloride transmembrane transport, and consecutively, involved in various biological processes. Encoded by the gene card (GCID) is GC06M032030, the official name of the gene is CLIC1, and it is located on the chromosome 6p21.33. Alternative names more rarely used are G6 or the original, NCC27 (nuclear chloride channel) (http//: www/genecards.org). The gene encodes a protein expressed in the nucleus, including nucleus membrane. The protein is also expressed in the cell membrane, and on occasion, in the cytoplasm. The cytoplasmic protein is soluble and the membrane most probably consists of a single transmembrane domain. Mutation in the CLIC1 gene induces loss of dimerization and abolish the ion transport activity (Littles et al, 2004).

FUNCTIONS

CLIC1 include a variety of proteins that regulate cell membrane stabilization, transepithelial transport, regulation of the cell volume and maintaining the intracellular pH. There is a large variety of biological processes in which CLIC1 protein is directly involved, like chloride transport, platelet aggregation, regulation of the transmembrane transport or signal transduction. The protein is inserted in the cell membrane to form chloride ion channels. The activity of such channels strongly depends on pH and it is involved in the regulation of the cell cycle (Valenzuela et al, 1997; Valenzuela et al, 2000; Tulk et al, 2002).

IMMUNOHISTOCHEMICAL EXPRESSION IN NORMAL TISSUES

Until now, a broad spectrum of normal human tissues has been investigated to test the immunohistochemical expression of CLIC1. The pattern of the final product of reaction in most of the cases was granular nuclear and/or continuous at the level of the plasma membrane. CLIC1 has not been demonstrated by immunohistochemistry in the central nervous system, and a weak to moderate positive reaction was noticed in endocrine tissues, pancreas, skin, testis, and liver. A strong expression was constantly found in the epithelium of the prostate, gallbladder, colon, placenta, heart, and tubular system of the kidney (Berryman and Bretscher, 2000).

EXPRESSION IN TUMOR CELLS AND SIGNIFICANCE

CLIC1 is expressed in a large variety of human tumors, including here both benign and malignant. Chen et al (2007) investigated the expression of CLIC1 in gastric cancer, and found that CLIC1 is up-regulated in 67.9% of patients. The CLIC1 expression in tumor tissues was increased by 1.95-fold in comparison with adjacent apparently normal mucosa. It was found that elevated CLIC1 expression was strongly correlated with lymph node metastasis, lymphatic invasion, perineural invasion, and pathological staging. Moreover, CLIC1 seems to have a prognostic significance, as the 5-years survival rate was lower for low expression, and significantly higher in patients with strong expression. Therefore, preliminary results indicate that overexpression of CLIC1 is a potential prognostic marker for gastric cancer.

Although CLIC1 is involved in the regulation of the cell cycle and cell proliferation, the significance of its expression in hepatocarcinoma is not clear. It was found that both CLIC1 protein and mRNA levels were higher in hepatocarcinoma tissue. By immunohistochemistry a strong expression was noticed in 81.2% of the cases, and correlated with distant metastasis, pTNM stage and poor survival (Zhang et al, 2013). Contrary to gastric cancer, the strong expression of CLIC1 in hepatocarcinoma cells seems to be a poor prognostic factor. This is supported by the study of Wei et al (2015) that found that knockdown of CLIC1 increased maspin expression, overexpression of CLIC1 decreased maspin expression and CLIC1 protein expression is significantly correlated with vascular invasion. This suggest a new mechanism of CLIC1-mediated control of hepatocellular carcinoma invasiveness by targeting maspin.

The significance of CLIC1 expression in pancreatic ductal carcinoma is even less known. Jin et al (2016) investigating 70 cases by immunohistochemistry found a higher expression in 67.1% in pancreatic ductal adenocarcinoma compared with 25.7% in the adjacent

control tissues. High CLIC1 levels were associated with grade and size of the tumor, but not with other clinicopathological parameters, including stage and metastasis. Although a multivariate analysis showed a decreased overall survival in CLIC1 positive specimens, larger series are necessary to demonstrate the relationships with lymph node and distant metastasis.

A POTENTIAL TARGET FOR THERAPY?

The large number of cases which overexpress CLIC1 makes this target very attractive for therapy. There is no previous experience in this field in human tumor pathology. On one hand, CLIC family is expressed in a large variety of normal tissue. On the other, many heterogeneous tumors overexpress CLIC1. Therefore, it is necessary to built a humanized selective antibody to act specifically on tumor cells.

PERSPECTIVES

Many issues related to CLIC1 expression in malignant tumors are virtually unknown. Although CLIC1 is expressed in a large variety of tumors, and usually with high incidence, its real prognostic role is not yet clear. This is why there are necessary other studies on large series of patients to clarify the relationships between CLIC1 and other clinical and pathological conventional prognostic factors. In some conditions, like in renal cell carcinoma, CLIC1 is expressed the large majority of the cases. An experimental model reproducing the effects of an CLIC1 antibody could bring interesting information about its effects on tumor cells.

CONCLUSION

Currently, CLIC1 seems to be expressed by a large variety of normal and pathological tissue. There were accumulated many data that support its prognostic role in human malignant tumors. If CLIC1 will become a target for therapy in the next coming years, it remains to be demonstrated.

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