

## Colon Cancer and Immunotherapy: CD40 Ligand as a Potential Therapeutic Target

Orfanos S<sup>1</sup>, Patelis N<sup>1\*</sup>, Davakis S<sup>1</sup>, Vailas M<sup>1</sup>, Damaskos C<sup>2</sup>, Margonis GA<sup>3</sup>, Pikoulis E<sup>1</sup> and Antoniou E<sup>2</sup>

<sup>1</sup>First Department of Surgery, Laiko General Hospital, National and Kapodistrian University of Athens, Athens, Greece

<sup>2</sup>Department of Propaedeutic Surgery, Laiko General Hospital, School of Medicine, University of Athens, Athens, Greece.

<sup>3</sup>Department of Surgery, The Johns Hopkins University School of Medicine, Baltimore

### Abstract

CD40, a member of the tumor necrosis factor (TNF) superfamily, it is broadly expressed on a variety of cells. There are studies to suggest that the expression of CD40 is correlated to several malignancies, while its innate therapeutic qualities are yet to be confirmed. Colon cancer is one of the most common cancers, while little can be done for the patients with advanced colon cancer even at the presence time. CD40 are present in the colon cancer, and are a possible therapeutic immunotherapy target in order to enhance the overall survival rates of the patients with advanced disease.

**Keywords:** Colon; Cancer; Immunotherapy; CD40; CD40 ligand

### Introduction

CD40 and its ligand CD40L (CD154), members of the tumor necrosis factor (TNF) super-family, have a key role in the functions of the immune system. It is well known that CD40 is widely expressed in monocytes, dendritic cells, endothelial cells, epithelial cells, platelets and fibroblasts. However, CD40 expression was observed not only in cells related to the immune system, but also in cells of several different types of carcinomas, such as in the ovary, breast, lung, renal, melanoma and colon among others. CD40 it appears to initiate the differentiation and the proliferation of certain cell types [1].

The CD40 ligand CD154 has been most commonly observed on activated CD4<sup>+</sup> T lymphocytes and secondly on activated CD8<sup>+</sup> T lymphocytes, eosinophils and B lymphocytes as well. Connection of the CD40 with its ligand CD154, results in the activation of both the humoral and cellular immune response systems via the professional antigen presenting cells (APCs) and T cells [2]. While some researchers suggest that CD40 expression on tumor cells act as possible receptors for mitogenic signals, it is proven that the CD154 on tumor cells results in growth inhibition and sensitization to apoptosis. Furthermore, the expression of CD40 in lung cancer is established as a crucial biomarker for the extension and the outcome of the disease [3].

### Methods-Search Strategy - Study Selection

A literature search was conducted in February 2017, in the PubMed electronic database, using the following search terms in different combinations: "CD40", "CD154", "Colon Cancer" and "Immunotherapy", "CD40 ligand". No limits were applied. Manual reference checks were performed on bibliographies of accepted articles. The aim was to identify relevant studies reporting possible effects and possibilities of CD40 and CD40 ligand as a therapeutic target for colon cancer. Initially, all the titles and abstracts were screened. Original articles were considered potentially eligible if they included clinical trials and experimental models trials. The authors then proceeded to read the full texts of the potentially eligible studies, applying inclusion and exclusion criteria. Studies that met the following criteria were selected: original articles, clinical trials, review articles, editorials and letters to editors.

### Results and Discussion

Epithelial cells usually respond to CD40 activation by cytokine

secretion, while fibroblasts and endothelial cells by increased proliferation. On the contrary, cell growth inhibition has been observed in an amount of malignancies following CD40 ligation by soluble antagonists (i.e., sCD40L) or antagonistic anti-CD40 antibody. Soluble antagonists are growth-inhibitory; they are weakly proapoptotic, unless protein synthesis is blocked using pharmacologic agents. CD40 ligation by membrane presented CD40L (mCD40L) on the other hand, induces extensive death in carcinoma cells without pharmacological intervention.

Colon cancer is one of the most common malignancies and one of the leading causes of cancer related deaths worldwide. Although progress in medicine in the recent past years is great, treatment of the advanced colon cancer still remains inadequate [4]. Nowadays, wide surgical excision combined with adjuvant or/and neo-adjuvant therapy is the gold standard therapy provided. As a result, newer approaches in systemic therapy are needed to improve the overall survival rate of the colon cancer patients. The most promising therapy towards this direction is tumor immunotherapy for colon cancer.

The immune system of tumor-bearing patients has failed to eliminate malignant tumors effectively, because either of a lack of recognizable tumor antigens or the inability of the tumor antigens to elicit an effective immune response. The aim of many immunotherapy approaches is to modify the microenvironment of the tumor antigen or the priming site such that inflammatory cytokines are generated and the target antigens are challenged into the APCs [5]. If the APCs express the appropriate co-stimulatory molecules, they could lead to enhanced presentation of tumor antigens to T cells and the activation of antitumor immune response as a result.

*Ex vivo* infection of tumor cells with the CD154 gene or *in vivo*

**\*Corresponding author:** Dr. Nikolaos Patelis, First Department of Surgery, Laiko General Hospital, National and Kapodistrian University of Athens, Athens, Greece, Tel: 302107456243; E-mail: [npatelis@gmail.com](mailto:npatelis@gmail.com)

Received February 23, 2017; Accepted March 14, 2017; Published March 17, 2017

**Citation:** Orfanos S, Patelis N, Davakis S, Vailas M, Damaskos C, et al. (2017) Colon Cancer and Immunotherapy: CD40 Ligand as a Potential Therapeutic Target. J Mol Genet Med 11: 253 doi:10.4172/1747-0862.1000253

**Copyright:** © 2017 Orfanos S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

infection of CD40L gene it has been shown induction of antitumor immunity against different tumor cell lines in subcutaneous experimental models. Furthermore, immunization with *in vivo* modified tumor cells that express CD154 can eliminate established tumors according to Tomonori I, et al. [6]. On the other hand, immunization with tumor cells that have been modified *ex vivo* to express CD154 it is not sufficient enough to eliminate an already established tumor in the clinical practice.

The antitumor effects caused by CD154 have shown long-term survival and resistance to rechallenge with parental tumor cells, signifying the persistent nature of the immune protection. This therapy not only eradicated the original colon cancer but also prevented metastasis to the lungs and the liver in the prevention mode [6]. Moreover, this therapy was very effective in the treatment model.

## Conclusion

CD40L immunogene therapy may indicate the possibility of being a new therapeutic option against colon cancer, metastatic to the liver or lung. Despite of the incomplete understanding of the biologic role of CD40 expression on tumor cells and its influence on the initiation on tumor growth, the large part of data is evidencing on its potential role as

a target for cancer immunotherapy. In addition, the evidence about the negative role of CD-40 ligation may be used as well for the development of means for its blocking.

## References

1. Koho H, Paulie S, Ben-Aissa H, Jonsdottir I, Hansson Y, et al. (1984) Monoclonal antibodies to antigens associated with transitional cell carcinoma of the human urinary bladder. I. Determination of the selectivity of six antibodies by cell ELISA and immunofluorescence. *Cancer Immunol Immunother* 17: 165–172.
2. Roy M, Waldschmidt T, Aruffo A, Ledbetter JA, Noelle RJ (1993) The regulation of the expression of gp39, the CD40 ligand, on normal and cloned CD4+ T cells. *J Immunol* 151: 2497-2510.
3. Sabel MS, Yamada M, Kawaguchi Y (2000) CD40 expression on human lung cancer correlates with metastatic spread. *Cancer Immunol. Immunother* 49: 101-108.
4. Ferlay J, Bray E, Pisani P, Parkin DM (2000) GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide. IARC Cancer Base, Lyon, IARC Press, France.
5. Grewal IS, Flavell RA (1998) CD40 and CD154 in cell-mediated immunity. *Ann Rev Immunol* 16: 111-135.
6. Lida T, Shiba H, Misawa T, Ohashi T, Eto Y, et al. (2010) Immunogene therapy against colon cancer metastasis using an adenovirus vector expressing CD40 ligand. *Surgery* 148: 925-935.