DOI 10.7603/s40730-014-0007-4

Biomedical Research and Therapy **2014, 1(2):35-36**
ISSN 2198-4093
www.bmrat.org

COMMENTARY

CD47 target: from theory to reality

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Received: 25 January 2014 / **Accepted**: 25 February 2014 / **Published online**: 22 March 2014

Abstract— Irving Weissman at the Stanford University School of Medicine in Palo Alto, California found that leukemia cells produced higher levels of CD47. This high expression help tumor cells to escape from the immune system. To date, the CD47 receptor becomes the interesting target in cancer treatment. Some recent studies from in vitro to pre-clinical trials showed that blocking CD47 by anti-CD47 or morpholino efficiently tumor cells or tumor growth. From these results, some clinical trials were suggested to test the safety and efficacy of anti-CD47 therapy. There is at least a clinical trial using anti-CD47 therapy registered in clinicaltrial.gov. Some other clinical trials will be performed at Stanford in the mid-2014 as well as in the United Kingdom.

Keywords— CD47, cancer targeting therapy, Immunotherapy, Gene therapy.

CD47 is a cell surface protein of the immunoglobulin (Ig), so-called integrin-associated protein (IAP). CD47 consists of an extracellular IgV domain, a five times transmembrane-spanning domain, and a short alternatively spliced cytoplasmic tail. There are four alternatively spliced isoforms of CD47 that differ only in the length of their cytoplasmic tail (Reinhold et al., 1995). CD47 can interact with some ligands such as thrombospondin-1 (TSP-1), signal-regulatory protein-alpha (SIRP alpha), and integrins. When TSP-1 binds to CD47 on the cell surface, it effects to some fundamental cellular functions included cell migration, adhesion, cell proliferation, apoptosis, and plays a role in the regulation of angiogenesis and inflammation. SIRPα causes leads to bidirectional signaling, resulting in different cell-to-cell responses including inhibition of phagocytosis, stimulation of cell-cell fusion, and T-cell activation; while integrin (most common integrin avb3) effects a range of cell functions including adhesion, spreading and migration on CD47 expressing cells.

In all roles of CD47, there is an important function related to the inflammatory response of CD47. Oldenberg et al. examined red blood cells lacking the CD47 proteins by injecting into normal mice, these cells were rapidly engulfed by the macrophages of the spleen, while red cells expressing CD47 were not taken up (Oldenborg et al., 2000). That means CD47 was a barrier to phagocytosis. In human, CD47 is highly expressed in hematopoietic stem cells (Jaiswal et al., 2009).

Recent years, some studies showed that CD47 is overexpressed in many types of human cancers (Chao et al., 2012). And this molecular is as a "don't eat me' signal. From literatures CD47 is considered as the marker of some cancers (Chao et al., 2012), and worse clinical prognosis (Majeti et al., 2009); besides, CD47 also was demonstrated that it related to tumor metastasis (Uluckan et al., 2009). In the normal cells, CD47 is expressed and these cells are protected from phagocytosis by dendritic cells and macrophages. Dendritic cells and macrophages expressed in the receptor SIRP-α that interacted with CD47 on normal cells. This interaction helps dendritic cells or macrophage recognize the normal cells. So that, by this way cancer cells also escape from killing of the immune system.

To break the mechanism that cancer cells escape from phagocytosis by dendritic cells and macrophage, almost efforts developed therapies to inhibit the CD47-SIRPα pathway. In the principally monoclonal antibodies directed against to CD47 is used to block interaction between immune cells and cancer cells.

From this theory, some studies used anti-CD47 monoclonal

antibody to block CD47 receptor and evaluate the efficacy anti-tumor in animal models. Majeti et al. (2009) showed human AML LSC-engrafted mice with anti-CD47 antibody depleted AML and targeted AML LSC (Majeti et al., 2009). In another model, Chao et al. (2012) developed in vivo lymphoma metastasis models (Chao et al., 2012) and using CD47 Mab to treat. They also showed that CD47 Mab inhibited formation of extranodal disease, inhibited hematogenous dissemination, inhibited chemokine-mediated migration of lymphoma cells (Chao et al., 2012). By this way, Kim et al. (2012) also inhibited the tumor growth in multiple myeloma mice models (Kim et al., 2012). Moreover, anti-CD47 therapies were not only successfully inhibit hematological malignancies but also efficiently decrease solid tumor growth. Several solid cancers were preclinically evaluated such as breast, colon, prostate, and bladder cancers, and sarcomas (Willingham et al., 2012). In the mice bearing human breast tumors, 100% mice formed breast tumors after injected with human breast cancer cells; while no tumors were palpable in the anti-CD47 Mab treated mice. Authors also considered that treating with anti-CD47 Mab mice had fully eliminated the breast cancer cells, including the CSCs (Willingham et al., 2012). In two additional xenotransplantation models of bladder and ovarian cancer, a substantial inhibition of tumor growth was observed in the majority of mice (Willingham et al., 2012). Anti-CD47 Mabs also suppressed sarcoma tumors, decreased the size and number of metastases (Edris et al., 2012).

These results pushed application of anti-CD47 Mabs into clinical trials. The first clinical trial registered in clinicaltrial.gov in this year (2014) with title "Phase I, multicenter, open-label, dose-escalating, clinical and pharmacokinetics study of humanized anti-CD47 antibody as the single agent in patients with advanced or metastatic solid tumors" (NCT02096770). In this study, patients will receive 10 mg/kg intravenously of anti-CD47 Mab over 30-90 minutes repeats every 21 days. Patients with advanced solid tumor malignancy or lymphoma (non-Hodgkin's or Hodgkin's lymphoma) will be enrolled in this study. Other groups at Stanford also are continuing to work hard preparing the groundwork for clinical trials using anti-CD47 Mab for cancer treatment. Maybe this clinical trial will apply in this summer. These are also the first clinical trials that will evaluate the safety in a very few patients.

With the amazing results in animal models, both scientists and cancer patients hope that these clinical trials will be successful and anti-CD47 Mab become novel therapy to treat cancers, especially advanced cancers.

Abbreviations

AML: Acute myeloid leukemia; IAP: Integrin-associated protein; Ig: Immunoglobulin; SIRP alpha: Signal-regulatory protein-alpha; TSP-1: Thrombospondin-1

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Cite this article as:

Wu, J. (2014). CD47 target: from theory to reality. *Biomedical Research And Therapy, 1*(2):35-36.