318 C/T polymorphism of cytotoxic T lymphocyte antigen-4 in allegic asthma: functional analysis by gene ontology

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Abstract

Cytotoxic T lymphocyte antigen-4 (CTLA-4) represents one of the most extensively studied receptors in the costimulatory pathway and has recently been shown to function as a potent inhibitor of T cell-mediated immunity. The association of CTLA-4 gene polymorphisms with allergic asthma is still controversial and therefore was the subject of this study. However, the role of the CTLA-4 318 C/T change needs a systematic theoretical explanation. However, studies on an association between this polymorphism and clinical findings have yielded some inconsistent findings. To study the functional aberration in the human wild and mutate types of CTLA-4 in pathogenesis is hard. Here, the author used a new gene ontology technology to predict the molecular function of human wild and mutate types of CTLA-4. Here, it can be seen that there is no functional difference between wild and mutate types of CTLA-4. This can support the null effect of this polymorphism in clinical findings of the patients. This polymorphism might not be an important factor and have null effect on cardiovascular disease.

Key words: *CTLA-4, polymorphism, function.*

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Introduction

Costimulatory pathway ligands and receptors can deliver either positive or negative signals to help determine the ultimate fate of activated T lymphocytes [1]. Cytotoxic T lymphocyte antigen-4 (CTLA-4) represents one of the most extensively studied receptors in the costimulatory pathway and has recently been shown to function as a potent inhibitor of T cell-mediated immunity [1]. The CTLA-4 molecule is an important negative regulator of T cell activation [2]. It is encoded on chromosome 2q33 and found to be associated with several allergic phenotypes including asthma [2]. Common polymorphisms of CTLA-4 include 318 C/T [1-3]. Lee et al said that the CTLA-4 promoter (-318 C/T) T allele may serve as a clinically useful marker of severe asthma [4]. However, Jasek et al found that CTLA-4 polymorphisms do not seem to be a risk factor for allergic asthma [2]. In addition, similar results were also reported by Nakao et al [5]. The association of CTLA-4 gene polymorphisms with allergic asthma is still controversial and therefore was the subject of this study.

However, the role of the CTLA-4 318 C/T change needs a systematic theoretical explanation. To study the functional difference due to gene polymorphism is hard. Luckily, the new development in bioinformatics can be applied in nanoscale genomics and proteomics research. Basically, genes in biological databases are linked to gene ontology terms, allowing biologists to ask questions about gene function in a manner independent of species [6]. Ontologies are fundamental knowledge representations that provide not only standards for annotating and indexing biological information, but also the basis for implementing functional classification and interpretation models [6]. Here, the author used a new gene ontology technology to predict the molecular function of human CTLA-4 318 C/T polymorphism.

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Material and Methods

Getting the sequence and mutation assignment

The database Pubmed was used for data mining of the amino acid sequence for human CTLA-4. Then the mutation assignment 318 C/T was performed.

Prediction of molecular function and biological process

The author performs prediction of molecular function and biological process of L55M in wild and mutate types using a novel gene ontology prediction tool, GoFigure [7]. GoFigure is an computational algorithm tool which is recently developed in gene ontology [7]. The tool accepts an input DNA or protein sequence, and uses BLAST to identify homologous sequences in gene ontology annotated databases [7]. The approach is to use a BLAST search to identify homologs in public databases that have been annotated with gene ontology terms [7]. These include: SwissProt, Flybase (Drosophila), the Saccharomyces Genome Database (SGD), Mouse Genome Informatics (MGI) and Wormbase (nematode) [7]. The processing algorithm is a measure of

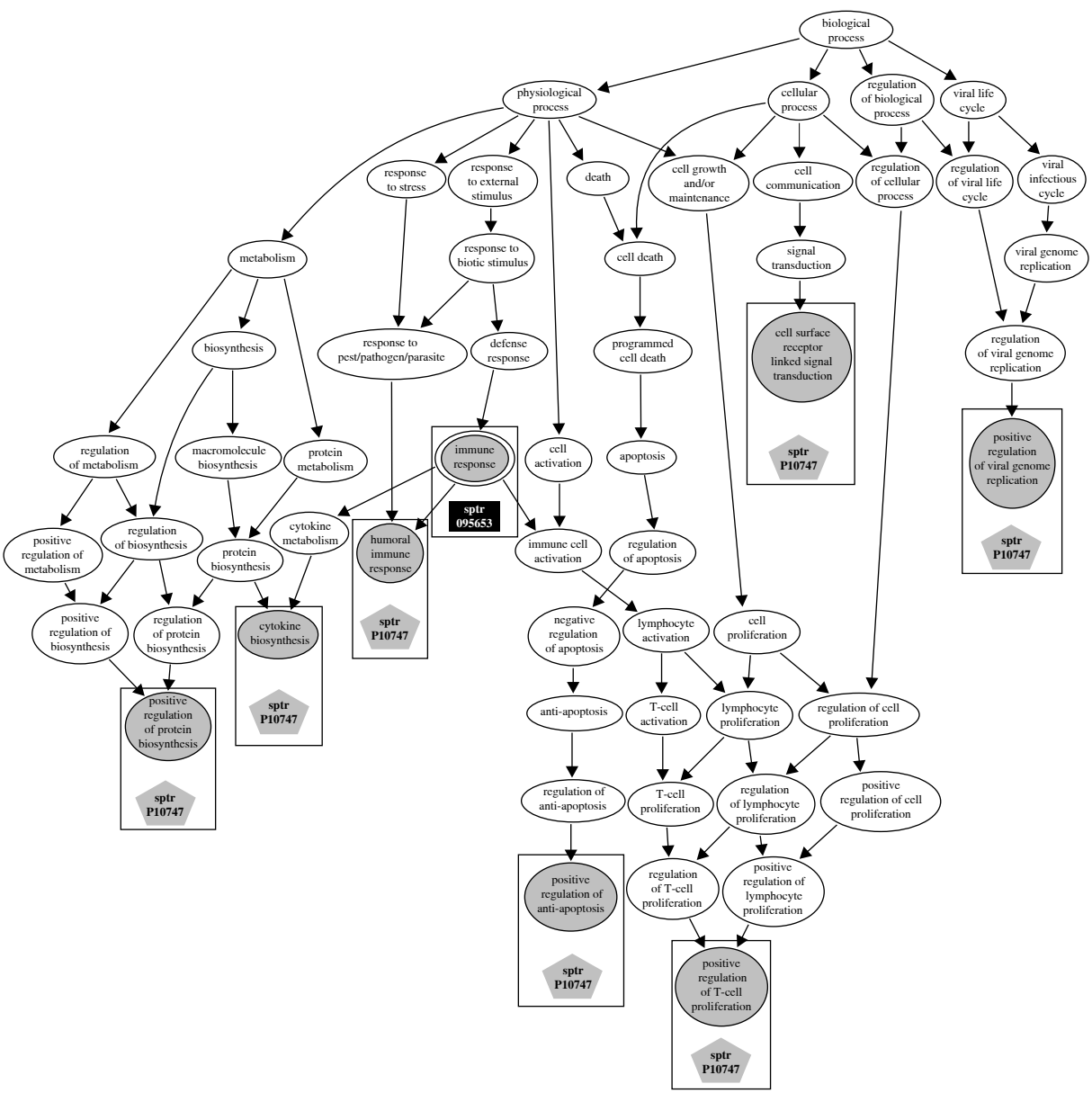

Fig. 1. Expected biological process of wild type of CTLA-4 (sptr number is the specific number within Swiss-Prot/TrEMBL database)

sequence similarity that is returned by BLASTing the unknown sequence against the GO annotated model organism databases [7]. GO evidence indicates the basis on which the BLAST hits returned in both quantity and quality aspects were annotated [7-8]. The validity and reliability of GoFigure tool are acceptable [7, 9]. The algorithm developed for GoFigure is especially designed for making Figures of closely spaced roundish objects such as cell nuclei in tissue [7]. The contents of the results will show results for molecular function as well as biological process of the studied protein [7]. The prediction of molecular function was presented.

Results

Sequence of human CTLA-4

From searching of the database, sequence of human CTLA-4 was derived and the mutation 318 C/T was performed.

Prediction of molecular function

Using GoFigure server, the molecular function of wild and mutate types of CTLA-4 is predicted. The expected biological process of human wild and mutate types of CTLA-4

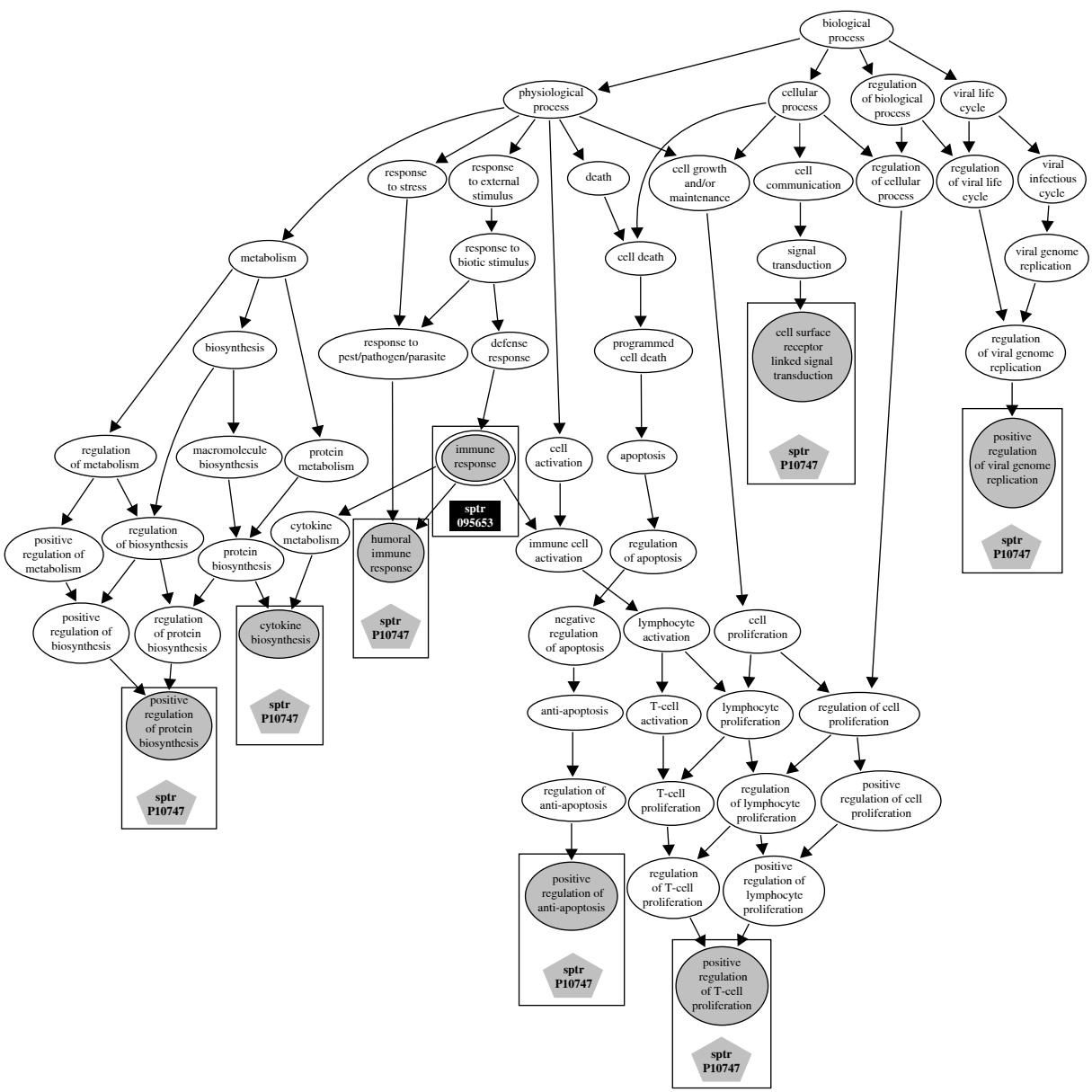

Fig. 2. Expected biological process of mutate type of CTLA-4 (sptr number is the specific number within Swiss-Prot/TrEMBL database)

are presented in figures 1 and 2. The molecular function of human wild and mutate types of CTLA-4 are same. The summary on the molecular function of human wild and mutate types of CTLA-4 is presented in table 1.

Discussion

The profound influence of CD28 and cytotoxic T-lymphocyte antigen-4 (CTLA-4) on T-cell immunity has been known for over a decade, yet the precise roles played by these molecules still continue to emerge [10]. Recent evidence suggests that CTLA-4 is also important in the homeostasis and function of a population of suppressive cells, termed regulatory T cells (Tregs) [10]. There are some published papers showing the association of CTLA-4 T(-107)C with clinical finding of allergic asthma [1-2]. However, there are some reports on the possible null effect of this polymorphism [4-5]. Clarification of the exact effect of this polymorphism is needed.

Based on the recent advance in the genomics technology, current microarray technologies permit the examination of gene expression patterns of tens of thousands of genes. One challenge facing the biologist interpreting such data is recognizing the function of many of the hits identified in a single experiment [7]. While one can check the literature, a rapid means to get some idea of potential function of a gene product is to obtain the ontology terms that describe the gene [7]. The gene ontology is developed for this specific purpose. Many genes ontology tools have been constructed and launched. Here, the author used a gene ontology tool to predict the function of human wild and mutate types of CTLA-4. The selected gene ontology tool is proved to be effective in prediction for the gene function such as the prediction of the leptin and leptin receptor system in the previous recent report by Wiwanitkit [11].

Here, it can be seen that there is no functional difference between wild and mutate types of CTLA-4. Therefore, there should be no difference in effect of wild and mutate types of CTLA-4. This can support the null effect of this polymorphism in clinical findings of the patients. Finally, the author hereby recommends for a further study to analyze other know genetic variants within CTLA-4 to add more knowledge in this area.

Table 1. The summary on the molecular function and biological process of human wild and mutate types of CTLA-4

	Wild type	Mutate type
molecular function	defense/immunity protein activity, protein binding, coreceptor activity	defense/immunity protein activity, protein binding, coreceptor activity

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