FUNDING PROGRAM FOR NEXT GENERATION WORLD-LEADING RESEARCHERS

Project Title: Research on regulatory mechanisms of allergic disease-related genes for prevention and treatment of allergic diseases	
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1. Background of research

Since allergic diseases, including pollinosis, atopic dermatitis, childhood allergy, and asthma, are observed at a disease rate over 30% among Japanese people and therefore the economic damage due to allergic diseases are huge, therapy for these diseases is gaining a matter of concern. However, most of current therapy are palliative.

2. Research objectives

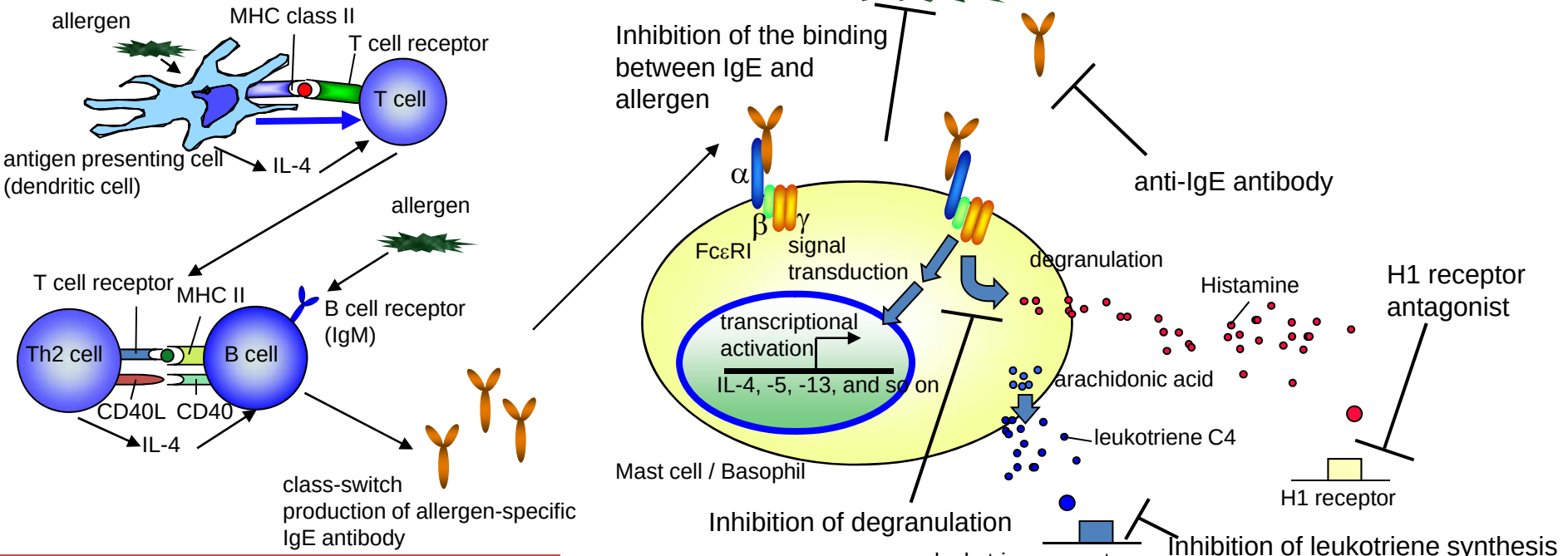
Allergen stimulates mast cells and basophils through the interaction between IgE antibody and the high affinity IgE receptor (FcεRI) on the effector cells to cause allergic reactions. Since most of currently-used anti-allergic drugs inhibit a series of reactions leading to the allergic diseases, the reactions caused by IgE-FcεRI interaction must be attractive targets for the treatment of allergy. In this research, we will focus on the pathway, "IgE-FcεRI-mast cells/basophils", which is common for various allergic diseases, and try to suppress the pathway by regulating the expression and/or function of FcεRI. Furthermore, we will try to elucidate the roles of transcription factors in immune system. For this purpose, we will analyze how the transcription factors regulate the expression of the allergic disease- and autoimmune disease-related key molecules for controlling the functions of effector cells.

3. Research characteristics (incl. originality and creativity)

The methodology to suppress of allergic reactions by the downregulation of FcεRI, a trigger of allergy, is a novel approach in allergic diseases. Because the transcription factors regulate allergic genes in a cell-type-specific manner in immune system, functional modulation of the transcription factors is expected to occur in a manner highly specific to allergic diseases. We try to obtain novel anti-allergic drugs by screening various materials originated from food and microbial metabolites. The expression mechanism of other allergy-related molecules are analyzed in a similar way by focusing the role of transcription factors. To evaluate the effects of congenital and environmental factors on allergic diseases, both nucleotide polymorphisms and epigenetic condition of related genes in allergic patients are analyzed.

4. Anticipated effects and future applications of research

It is expected that the system to screen for the compounds that inhibit the expression of allergy-related molecules, including FceRI, will be established in early stage and the effective materials will be obtained by using this system. The identification of allergy-related genes by analyzing the nucleotide polymorphisms provides the information on tailor-made treatment of allergy. The analysis of chromosomal condition affected by the environment will lead a new therapeutic approach. These findings and methods are applicable in various immune-diseases, by targeting other immune-related cells, such as dendritic cells, T cells, and B cells.



Background and objectives of research

Schematic drawing of type-I allergic reaction

Cross-linking of IgE receptor (FcεRI) by binding of multivalent allergen to IgE antibody induces rapid activation of mast cells and basophils resulting in allergic responses.
In this program, roles of transcription factors in the regulation of allergic-related gene expression and cell function are analyzed. We also try to find the new drug to treat or prevent allergic diseases by the screening system established from our findings.
Briefly, we analyze the regulation mechanism of expression of the allergy-related molecules including IgE receptor, and functions of mast cells, basophils, and dendritic cells.

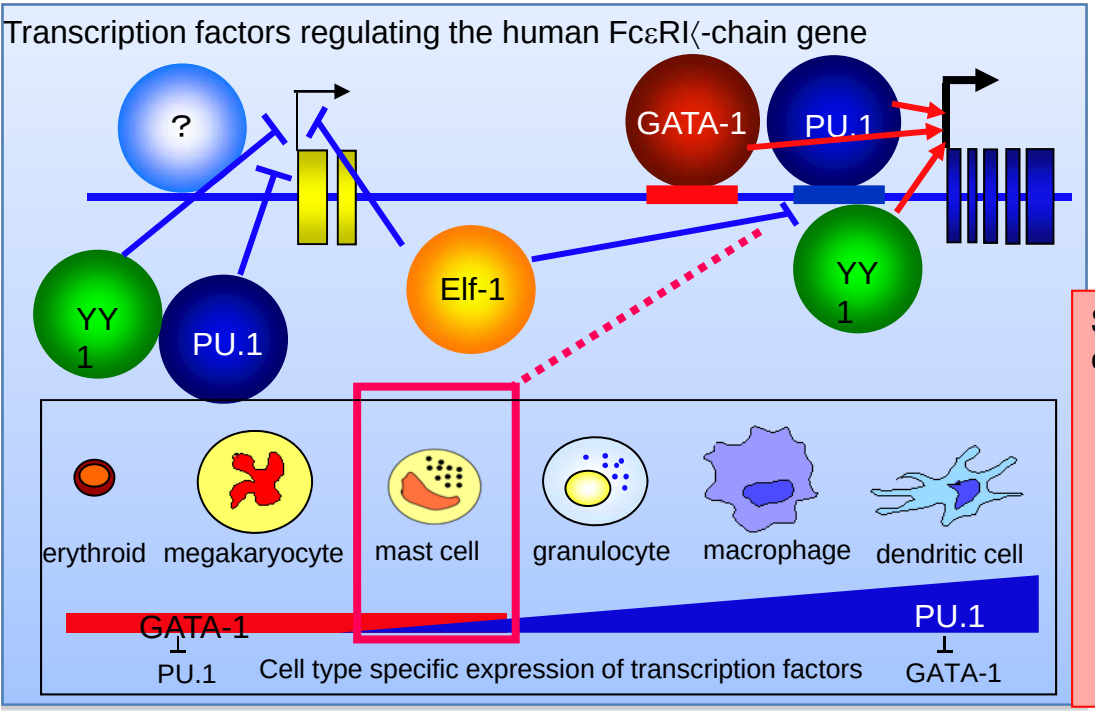
Research scope

Regulation mechanism of FcεRI gene expression is revealed.
Transcription factors, which control FcεRI expression, is identified.
Roles of identified transcription factors in the function of mast cells and/or basophils are clarified.
In a similar way, the roles of key transcription factors in various immune-related cells including dendritic cells, T cells, and B cells will be revealed.
These findings are useful to control the function of hematopoietic cells involves in allergic- or autoimmune-diseases.
Nucleotide polymorphisms, which associate with risk of allergy, are identified.

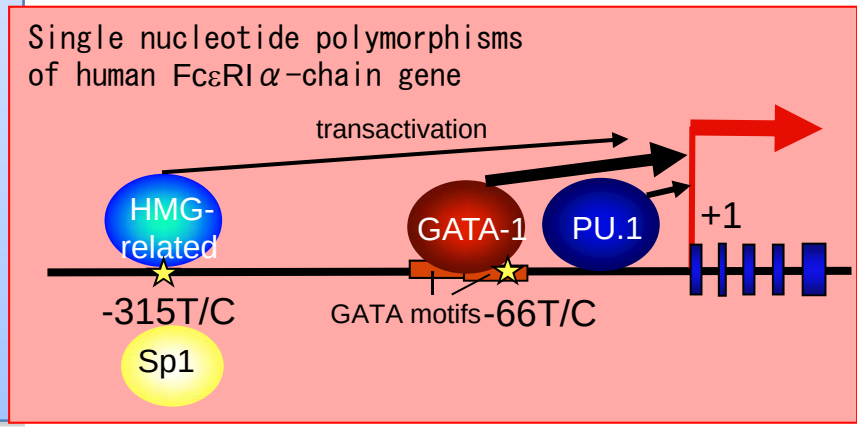
Anticipated effects and future applications of research

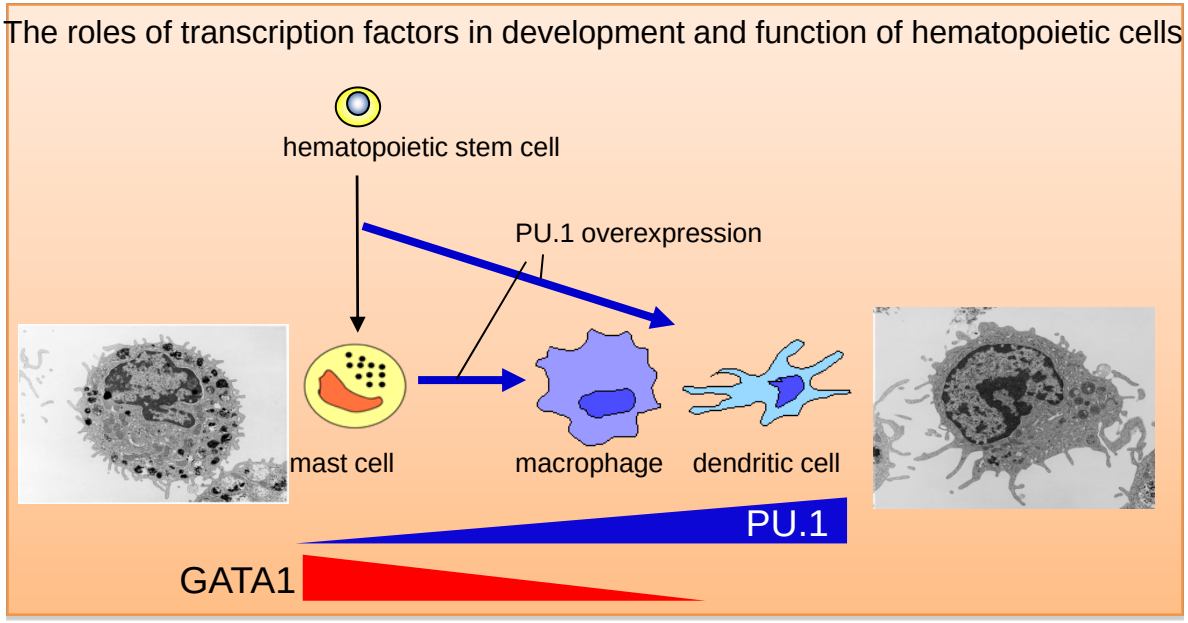
Based on these findings, novel materials that suppress the expression or function of allergy-related molecules will be found.
The information of candidate genes, which increase the risk of allergic and autoimmune diseases, will be obtained.

Research characteristics: The studies regarding transcription factors (based on our previous findings)



- Mechanism of mast cell-specific cooperation between GATA1 and PU.1
- Identification of transcription factors regulating mast cell- and basophil-specific gene expression





- Association between allergic diseases and polymorphisms in the genes encoding FcεRI subunits
- Effect of polymorphisms on the function of allergy-related genes
- Comparative search for allergy-related polymorphisms in Japanese and European populations

- The role of PU.1 in gene expression and function of dendritic cells
- Treatment of autoimmune disease by regulation of PU.1 function
- The roles of hematopoietic cell-specific transcription factors