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Hypothesis

A novel hypothesis for the gene expression for the control of atopic and other hereditary diseases

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ABSTRACT

The requirement of RNA polymerase proteins and transcription factor proteins for the expression of genetic information in DNA clearly indicates that the process is influenced by certain proteins in the body and/or in the environment, which is totally opposite to the 'central dogma' of Crick. In this article, we present a working hypothesis (helical hypothesis) that may explain the programmed nature of various biological events simply and naturally. Future investigations on the factors that regulate the gene transcription of cytokine clusters, including intereukin (IL)-4 and IL-5, may provide an answer for controlling atopic as well as other hereditary (genetic) diseases.

Key words: asthma, atopic dermatitis, atopy, central dogma, gene expression, hereditary disease.

Atopic diseases have been recognized to be hereditary and extensive investigations to identify so-called 'atopy genes' have been performed.[1,3] An association between high serum IgE and the polymorphism in the β chain of the high-affinity IgE receptor was first described by Hopkin and colleagues.[1] Marsh and colleagues found evidence for linkage of markers on chromosome 5q with a gene controlling total serum IgE levels, but not specific IgE antibody concentration.[2] More recently, Rosenwasser and colleagues reported genetic polymorphism in the interleukin (IL)-4 promoter gene associated with enhanced IgE levels.[3]

We have recently suggested that eosinophilic inflammation in atopic diseases, such as chronic bronchial asthma and atopic dermatitis, may be induced by hyperproduction of IL-5, which is the result of enhanced IL-5 gene transcription.[4–6] In Japan and in Western countries, the prevalence of atopic diseases has been increasing year by year. For the management of atopic (as well as many other genetic) diseases, an understanding of the mechanisms of gene expression is mandatory.

Genetic information consists of certain series of DNA and a fertilized egg develops step-by-step, apparently mimicking systemic evolution. In 1958, Crick proposed the 'central hypothesis', which suggested that all genetic information is transmitted from DNA to RNA and from RNA to proteins and never in reverse.[7] Findings using retroviruses and reverse transcriptase suggest that the central hypothesis may not always be compatible. Furthermore, it is known that the transcription of DNA is dependent on signals delivered by certain proteins (transcription factors). It is known that there are three kinds of RNA polymerase protein that produce RNA using DNA as templates.

In eukaryotic cells, the TATAAA sequence upstream of genes often acts as a promoter that determines the starting point of transcription. There are many proteins with activities different from RNA polymerases but that participate in transcription processes and we have termed these proteins 'transcription factors'. It is known that some proto-oncogene protein products, such as Fos and Jun, are actually transcription factors. Gene transcription is prominently influenced by the proliferation and developmental stage processes of cells, nutrition and the micro- and macroenvironments. The existence of RNA polymerase proteins and transcription factor proteins clearly indicates that the expression of genetic information in DNA is influenced by certain proteins and environmental factors.

The presence of biological phenomena, such as enzyme induction, endocrinological feedback system, immunological memory (secondary response), growth,

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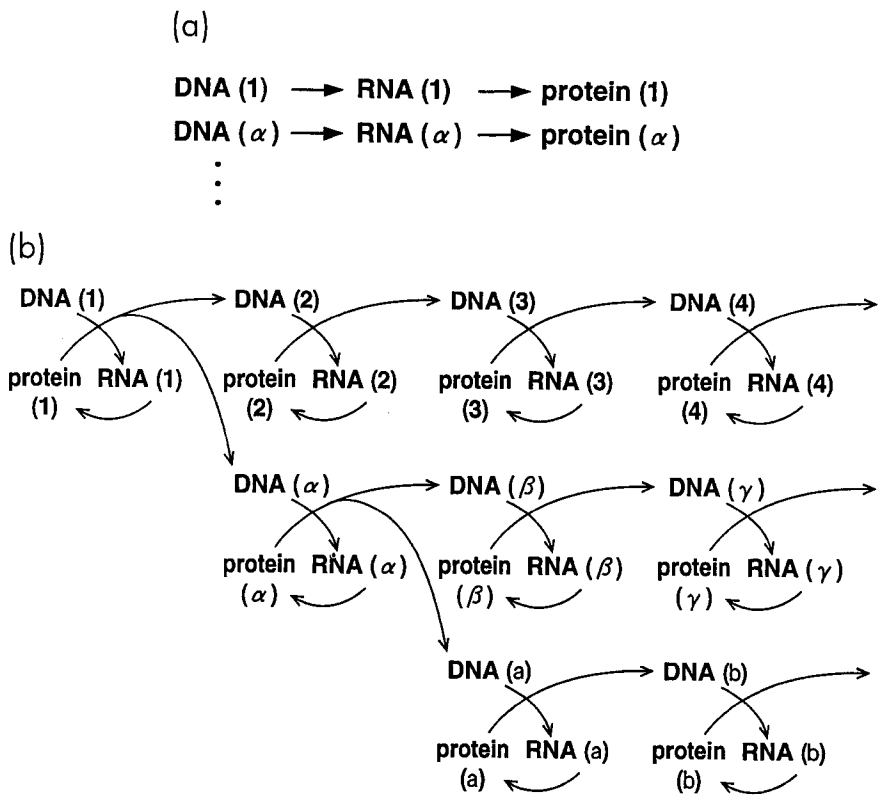

Fig. 1 Comparison of the central (a) and helical (b) hypotheses.

aging and apoptotic death etc., also clearly suggests that expression of genetic information is influenced by certain protein molecules and/or environmental factors, which is totally opposite to the 'central dogma'. Linearity of the central hypothesis gives little understanding of the programmed expression of biological events such as growth, aging and death. Thus, we have tried to derive a working hypothesis (helical hypothesis) that may explain the programmed nature of such biological events. The helical hypothesis proposes that product(s) of simple and primitive organisms induce expression of genes of an organism that is, in evolutionary terms, 'one step up', acting as transcription factor(s) or creating the appropriate microenvironment. Continuation of such processes would lead to gene expression and development of a complex and highly evolved organism, such as humans (Fig. 1).

The cause of the recent sharp increase in the number of atopic patients is unknown at present; however, future investigations to identify factors that promote the gene transcription of cytokine clusters, including IL-4 and IL-5, may provide an answer for controlling atopic as well as other hereditary (genetic) diseases.

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