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Xenobiotic-induced autoimmunity and protein aggregation diseases share a common subnuclear pathology

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Abstract

The cell nucleus constitutes a prime target of idiopathic and xenobiotic-induced autoimmunity. Despite of the high prevalence of rheumatic autoimmune diseases, the molecular mechanisms inducing systemic autoimmunity are largely unknown. In appreciation of Rudolf Virchow's cellularpathology, this review introduces the new concept of subnuclear pathology to autoimmune responses against the cell nucleus. Aberrant nucleoplasmic clusters consisting of nuclear autoantigens and proteasomes are observed in xenobiotic-treated cell lines, splenic cells from animal models of xenobiotic-induced autoimmunity, and dendritic cells of scleroderma patients. Aggregation of nuclear proteins in clusters inhibits nuclear functions such as replication and transcription, and induces altered proteasomal degradation of nuclear autoantigens and cellular senescence. Since these modifications of nuclear structure, function and proteolysis resemble the pathology of neurodegenerative protein aggregation diseases, the hypothesis is put forward that xenobiotic-induced autoimmunity may also be a consequence of protein aggregation.

Keywords: Autoimmunity; Cell nucleus; Neurodegenerative diseases; Protein degradation; Ubiquitin–proteasome system

Contents

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1. Introduction

The quest for discovery of molecular mechanisms that are involved in the pathology of diseases has fascinated generations of researchers. This research goal is so attractive because once a disease pathology is elucidated at the molecular level, specific treatment can be developed and in some cases respective information of the healthy population may serve in disease prevention after all. Resolution of biomedical research techniques increased significantly over the past two centuries, and still does. Contemporary research is characterized by fusion of disciplines such as biochemistry, molecular biology, and cell biology that enables functional characterization of morphological data. Such an interdisciplinary approach allows not only the dissection of biological processes into their consequent steps, but also the localization of these events within the cell.

As early as 1858, Rudolf Virchow founded contemporary pathology by attributing a fundamental role in the generation of diseases to cells (Cellularpathology, [1]). The cell nucleus represents a key player in eukaryotic lives and disease pathology, since it harbors the genetic information and the first steps in gene expression, namely replication, transcription and RNA maturation. The importance of the cell nucleus for the development of multicellular organisms was already appreciated in the nineteenth century by Robert Brown (see http://www.sciences.demon.co.uk/wbbrownb.htm). Consistent with this concept, it seems obvious that disturbances of nuclear structure and function cause developmental defects and/or disease. The emerging view is that the nucleus represents a dynamic, self-organizing structure consisting of substructures (domains, compartments) that form in response to the requirements of gene expression [2]. A paradigm for the formation of such substructures is the nucleolus that is assembled when transcription of genes encoding ribosomal RNA (rRNA) resumes after cell division, and is disassembled when transcription ceases during prophase [3]. Similar function-dependent clusters of nuclear proteins have been observed during transcription of mRNA in the nucleoplasm, DNA replication/recombination/repair, and processing of mRNA.

However, the dynamic properties of the cell nucleus may come at a price. Environmental changes may stress cells and induce alterations of nuclear structure and function that eventually cause generation of diseases. In appreciation of Virchow's Cellularpathology, we term such alterations of the functional architecture of the cell nucleus subnuclear pathology [4]. The present review describes unique clusters of nuclear proteins as a subnuclear pathology that can be observed in superficially distinct disorders such as xenobiotic-induced autoimmunity and protein aggregation diseases.

2. Subnuclear pathology of xenobiotic-induced autoimmunity

The cell nucleus is a prominent target in systemic autoimmune disorders since patients develop autoantibodies against nuclear proteins, and complexes thereof. Approximately 2% of the population in Europe and North America suffers from systemic, rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren's syndrome, and scleroderma [5]. Despite of its high prevalence, the molecular mechanisms of systemic autoimmunity are still unknown. Contributing factors that are discussed include (i) genetic predisposition, (ii) influence of hormones, and (iii) environmental factors. The latter are mainly correlated with the generation of scleroderma. Xenobiotic-induced subsets of this disorder have been observed in individuals exposed to silica(SiO_2)-dusts, organic solvents, heavy metals and certain drugs [6].

In order to elucidate molecular mechanisms of disease pathology, animal models of xenobiotic-induced autoimmunity were developed as elegant tools that enable controlled induction of antigen-driven autoimmune responses. Since antigen processing and presentation constitutes the basis for every antigen-driven autoimmune response, effects of xenobiotics on degradation of nuclear autoantigens have been analysed to identify molecular mechanisms of autoimmunity that targets the cell nucleus. By means of cell-based disease models, it has been shown that xenobiotics such as mercury chloride, platinum salts and the anti-cancer drug camptothecin specifically alter structure, function and proteolysis in the cell nucleus: Signature proteins of the cell nucleus redistribute to aberrant, nucleoplasmic clusters, where