Poly(ADP-ribosyl)ation in relation to cancer and autoimmune disease

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Abstract. Carcinogenesis involves multiple steps and pathways with functional alterations in a variety of genes. There is accumulating evidence that a deficiency of poly(ADP-ribose) polymerase (PARP)-1 leads to DNA repair defects, genomic instability, failure of induction of cell death and modulation of gene transcription. PARP-1 also supports the growth of tumor cells in certain situations. Genetic analyses of the PARP-1 gene have demonstrated alterations in neoplasms, and a mutation affecting the conserved amino acid E251 in germ cell tumors, as well as an association of a single-nucleotide polymorphism V762A with risk of prostate cancer. Recent development of a selective inhibitor of poly(ADP-ribose) glycohydrolase (PARG), the enzyme primarily responsible for degradation of poly(ADP-ribose), and PARG-deficient animals should facilitate studies of the relationship of poly(ADP-ribose) with carcinogenesis. Inhibitors of PARP have also suggested roles in the pathogenesis of autoimmune disease, and a promoter haplotype of PARP-1 confers a higher risk of rheumatoid arthritis. Further analysis of PARP-1, PARG and other PARP family genes should extend our understanding of the pathogenesis of cancer and autoimmune diseases. Furthermore, there is potential for sensitization to chemo- and radiation therapy of cancers as well as the treatment of autoimmune disease with development of stronger PARP inhibitors.

Key words. Poly(ADP-ribose); PARP; PARG; cancer; autoimmune diseases.

Introduction

Since the discovery of poly(ADP-ribose) and poly(ADP-ribose) polymerase (PARP) in the 1960s, progress in understanding their biological functions has been slow. The first breakthrough was made through the availability of a specific PARP inhibitor, 3-aminobenzamide (3AB), which was found to enhance the effects of DNA damaging agents [1]. The elucidation of the molecular mechanisms of DNA repair, DNA replication and transcription places the science of poly(ADP-ribose) and PARP on a firm basis with detailed information about their biological roles. Involvement of poly(ADP-ribose) and PARP in carcinogenesis has thereby become evident (fig. 1). The usage of appropriately designed inhibitors of PARP and knockout animals has been crucial. We previously published two review articles on carcinogenesis and PARP [2, 3]. In the present review, we include more recent information with relevance to human health, and cover priorities for future work.

In 1977, our group reported the presence of an antibody against poly(ADP-ribose) in the sera of patients with systemic lupus erythematosus (SLE), soon after the discovery of poly(ADP-ribose) and PARP [4]. This was followed by a demonstration of antibodies against poly(ADP-ribose) in the sera of New Zealand mice, which spontaneously develop autoimmune disease. The latter half of this paper reviews current information on research into poly(ADP-ribose) with reference to autoimmunity. Cancer and autoimmune diseases are clearly very different in their clinical features. Nevertheless, to a certain extent, the common involvement of poly(ADP-ribose) and PARP has been found. It can be envisaged that attention to both diseases, focusing on poly(ADP-ribose), would provide new insights. In this article, we summarize and discuss the current understanding of the relation of
poly(ADP-ribose) metabolism to pathogenesis and therapeutic aspects of cancer and autoimmune diseases, focusing on two major molecules, PARP-1 and PARG.

Cancer and autoimmune diseases

The development of cancer is governed by two groups of etiologic factors: heritable and environmental, namely genotoxic agents, such as DNA damaging agents, and non-genotoxic factors, such as hormones [5]. Cancers showing early onset are often associated with a substantial contribution of heritable genetic alteration, while those developing at an advanced age may be triggered by a combination of weak heritable and multiple environmental factors. DNA damage can be induced by chronic or acute inflammatory reactions and cause genetic and epigenetic changes in oncogenes and tumor suppressor genes. When caretaker genes for genomic stability are involved, evolution of tumors would be expected to be markedly accelerated.

Meanwhile, the pathogenesis of autoimmune diseases involves the activation of B and/or T cells, which recognize weak self-antigens and subsequent inflammation, which trigger damage in tissues. Delayed clearance of apoptotic cells by macrophages and dendritic cells is considered to stimulate immune responses to self-antigens, thereby leading to autoimmunity. Substantial involvement of heritable factors is also notable in autoimmune diseases. Hereditary defects may promote failure of T cell regulation, which is critical to support non-responsiveness to weak self-antigens. Environmental factors such as infection by microbes, ultraviolet (UV) radiation, ionizing radiation or drugs that modify weaker antigens might increase specific B or T cell activation.

Inflammation reactions are considered to promote carcinogenesis by inducing genomic instability due to oxidative and nitrosative stress on cellular components [6]. However, in general, organ-specific autoimmune diseases only infrequently predispose to cancer development. Deficiency in poly(ADP-ribose) polymerase (PARP)-1 might contribute to carcinogenesis through induction of genomic and epigenetic instability and alteration of transcriptional regulation and differentiation. In the pathogenesis of autoimmune diseases, PARP-1 dysfunction could modulate immune responses through affecting transcriptional regulation and might also influence cell death induction and clearance of dead cells.