Systemic Clearance of Radiation-Induced Apoptotic Cells by SIGN-R1 and Complement Factors and their Involvement in Autoimmune Diseases

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Abstract
Although ionizing radiation has been used for treating a variety of human cancers, radiotherapy inadvertently results in the damage of normal tissues, functionally altering the immune system and being able to cause various organ specific autoimmune diseases. Macrophages and complements play pivotal roles in the clearance of the apoptotic cells, facilitating their opsonin-dependent phagocytosis and systemic clearance of apoptotic cells. SIGN-R1, a membrane bound C-type lectin expressed on the splenic marginal macrophages, mediates a classical but C1q-independent complement activation pathway by interacting with C1q, and SIGN-R1 and complement factors might play the integral role in the clearance of radiation-induced apoptotic cells. Also, DC-SIGN, the human homolog of SIGN-R1 on dendritic cells and macrophage subpopulations, directly binds to C1q, probably providing an initiation site for the classical complement pathway in the presence of a pathogenic surface. Autoimmune diseases are becoming a serious public health problems and there is increasing evidence that C-type lectins and complement system are involved in the pathogenesis of the autoimmune diseases. Therefore, further works are required to identify the existence of diverse membrane-bound C-type lectins that could mediate complement activation against apoptotic cells in vivo and its involvement in the pathogenesis of the autoimmune diseases.

Keywords: Innate immunity; C-type lectins; SIGN-R1; DC-SIGN; Apoptotic cell clearance; Autoimmune disease

Introduction
Over the last century, radiotherapy has been used for treating a variety of human cancers [1]. Although the aim of radiotherapy is to induce apoptotic and non-apoptotic cell death in cancer cells, radiotherapy inadvertently results in the damage of normal tissues [2-4]. Among tissues, lymphoid organs including the lymph nodes, thymus, and spleen, are highly radiation-sensitive [5]. Thus, radiation treatment is able to raise side effects such as alteration of the immune system and broken self-tolerance against apoptotic cells, causing inflammatory and various organ specific autoimmune diseases such as gastritis, thyroiditis, and orchitis [6]. Furthermore, delayed clearance of apoptotic cells have been also linked with various inflammatory diseases and autoimmune diseases such as atherosclerosis, systemic lupus erythematosus, and rheumatoid arthritis [7-10]. Therefore, the rapid clearance of apoptotic cells is important for maintaining tissue homeostasis and for promoting an anti-inflammatory response in an effort to prevent an immune response against self-antigens.

SIGN-R1 is a transmembrane C-type lectin which is the murine homolog of human dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN, CD209) and highly expressed on a subpopulation of splenic marginal zone macrophages [11-13]. SIGN-R1 directly binds to C1q and mediates the opsonization of C3 on blood-borne Streptococcus pneumoniae, dominantly regulating the immunoglobulin-independent classical complement pathway [14]. Also, SIGN-R1 directly binds to apoptotic cells, being enhanced by interacting with C1q [3]. And then, the SIGN-R1–C1q complex immediately mediates C3 deposition on apoptotic cells, thus promoting their systemic clearance and maintaining immune tolerance in vivo (Figure 1) [3].

Macrophages are the primary cells taking the clearance of the apoptotic cells [15]. The recognition and clearance of apoptotic cells by these macrophages activate tolerogenic pathways in an effort to prevent an immune response against self-antigens [16]. The impaired clearance of apoptotic cells may lead to the induction of inflammation or trigger autoimmune disorders [16] such as rheumatoid arthritis, systemic lupus erythematosus, glomerulonephritis, and atherosclerosis [8-10,17]. Also, complement C3 contributes to the opsonization of apoptotic cells [18] and facilitates their opsonin-dependent phagocytosis, thus promoting their systemic clearance of apoptotic cells and maintaining immune tolerance in vivo [19,20]. In addition, complement receptor-mediated phagocytosis optimizes the uptake of apoptotic cells and instructs DCs to induce immune tolerance [21]. Also, the phagocytosis by macrophages is facilitated by direct binding of C1q and mannose binding lectin (MBL) to apoptotic cells [22-26]. Because C1q-deficient mice lead the impaired clearance of apoptotic cells [17] and C1q-deficiency in mice or humans is strongly susceptible to autoimmune diseases, C1q may play an important role in the apoptotic cell clearance [27].

After 4-6 hours post-irradiation, there was a transient and rapid increase of proteins, including SIGN-R1, C4, C3, and other complement factors in vivo [28,29], implying that complement activation could be caused by the recognition of radiation-induced apoptotic cells by SIGN-R1 [30]. In fact, SIGN-R1 dominantly activate the classical complement pathway for the clearance of apoptotic cells [19], leading for SIGN-R1+ macrophages to play an important role in the systemic clearance of radiation-induced apoptotic cells in vivo [31]. Therefore, the primary increase of complement C4 and C3 along with the increase of SIGN-R1 and the activation of SIGN-R1+ macrophages especially in the splenic marginal zone provide the optimal condition for SIGN-R1 to rapidly mediates the systemic clearance of a number of radiation-induced apoptotic cells in vivo [31].
It was suggested that DC-SIGN, the human homolog of SIGN-R1 on DCs and macrophage subpopulations, directly binds to C1q, the C1q–DC-SIGN complex could provide an initiation site for the classical complement pathway in the presence of a pathogenic surface [32]. C1q directly binds to apoptotic cells and belhs induces complement activation [25]. Therefore, it could be speculated that the C1q–DC-SIGN complex might also mediate the classical complement pathway and accelerate C3 deposition on radiation-induced apoptotic cells, thus enhancing the systemic clearance of apoptotic cells and maintaining immune tolerance in vivo. This hypothesis is valuable to integrate the role of DC-SIGN in apoptotic cell clearance by linking the recognition of apoptotic cells, their opsonization of complements, and the induction of immune tolerance.

Conclusion

Autoimmune diseases are a serious public health problems [33] and there is increasing evidence that C-type lectins and complement system are involved in the pathogenesis of the autoimmune diseases [34-38]. We introduced the new systemic clearance mechanism of radiation-induced apoptotic cells, in which SIGN-R1 could initiate and enhance the clearance of apoptotic cells by activating the complement deposition pathway against apoptotic cells in vivo and their involvement in the generation of autoimmune diseases, leading to the development of new biomarkers and diagnosis of autoimmune diseases.

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References


