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Review article

Amyloid and immune homeostasis

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ABSTRACT

Extracellular amyloid deposition defines a range of amyloidosis and amyloid-related disease. Addition to primary and secondary amyloidosis, amyloid-related disease can be observed in different tissue/organ that sharing the common pathogenesis based on the formation of amyloid deposition. Currently, both Alzheimer's disease and type 2 diabetes can be diagnosed with certainly only based on the autopsy results, by which amyloidosis of the associative tissue/organ is observed. Intriguingly, since it demonstrated that amyloid deposits trigger inflammatory reaction through the activation of cascaded immune response, wherein several lines of evidence implies a protective role of amyloid in preventing autoimmunity. Furthermore, attempts for preventing amyloid formation and/or removing amyloid deposits from the brain have caused meningoencephalitis and consequent deaths among the subjects. Hence, it is important to note that amyloid positively participates in maintaining immune homeostasis and contributes to irreversible inflammatory response. In this review, we will focus on the interactive relationship between amyloid and the immune system, discussing the potential functional roles of amyloid in immune tolerance and homeostasis.

1. Introduction

Under certain conditions, peptides and/or proteins can convert from soluble state into insoluble aggregates, contributing to the pathogenesis of amyloidosis and neurodegenerative disorders (Chiti and Dobson, 2006). Extracellular amyloid deposition as the major characteristics of amyloidosis and other diseases accompanied amyloid deposition remains many unrevealed functional roles (Pepys, 2006). However, the endoplasmic reticulum (ER) is a specialized organelle orchestrating the synthesis, folding and transport of most proteins in enkaryotic cells. Various environmental stresses can disrupt the ER protein-folding homeostasis, and trigger the intracellular signaling pathways intersecting at many levels with the immune system (Wang and Kaufman, 2016; Janssens et al., 2014). It is of great importance to recognize that amyloid-like protein folding is subject to stringent quality control systems. Yet, protein folding in ER is inefficient due to a substantial polypeptides failing to reach its native state but bringing toxic effects to the cell (Smith et al., 2011). Currently, besides the choice of combined chemotherapy for the treatment of amyloidosis, effect of anti-inflammatory therapy depends on the nature of the underlying inflammatory disorders (Wechalekar et al., 2016). However, improved outcomes have become to compromise the emerging regressive effect caused by immunotherapeutic targeting, implying amyloid is a multifaceted player in human health and disease (Johansson et al., 2016). Substantial evidence indicates that amyoid is associated with various types of immune responses to play a crucial role in the immune system and tissue homeostasis. Hence, we summarize the current knowledge and advanced understanding regarding the determinant role of amyloid in immune homeostasis, as well as maladaptive inflammatory response leading to amyloid disease and other amyloid-relevant disease. Notably, the present review will focus on the detailed functional roles of amyloid in immune response characterized as autoimmunity and anti-inflammatory response. This study highlights that having a profound understanding in the underlying interactive mechanism between amyloid and the immune system provides research directions on the opportunities and difficulties when targeting key therapeutic points for the treatment of these devastating chronic diseases in clinical practice.

2. Amyloid and inflammation

2.1. Amyloidosis and amyloid-related disease

The amyloidosis consists of a variety of heterogeneous diseases that characterized as the deposition of misfolded extracellular protein. However, amyloid deposits are discriminated from other pathogenic fibrils through binding to Congo red stain and, to date, more than 30 types of proteins contribute to the pathogenesis of amyloidosis (Leung et al., 2012). Amyloid deposits are rich in β-sheet structure and these rigid, nonbranching fibrils usually represent the clinical feature of amyloidosis (Merlini and Bellotti, 2003). There is no direct pathological

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Table 1
Clinical presentation of amyloidoses.

	Precursor protein	Disease	Location or comment
Localised amyloidosis	Immunoglobin light-chain (monoclonal B-cell dyscrasia)	Localised light-chain amyloidosis	Urinary tract, respiratory tract, larynx, skin and eyelids.
Hereditary systemic amyloidosis			
	Transthyretin	Prototypical FAP	
	ApoAI/II		Liver, kidney and heart.
	Gelsolin	Finnish hereditary amyloidosis	
	Lysozyme		Kidney, liver and spleen.
	Fibrinogen Aα chain		Kidney
	Cystatin C	Icelandic hereditary cerebral amyloid angiopathy	Brain
Acquired systemic amyloidosis			
	Immunoglobin light-chain (monoclonal B-cell dyscrasia)	Systemic light-chain amyloidosis	Primary amyloidosis, myeloma-associated.
	SAA	AA amyloidosis	Secondary amyloidosis or reactive amyloidosis.
	Immunoglobin (monoclonal B-cell dyscrasia)	Pulmonary small cell carcinoma	Lung
	β2-microglobulin	Chronic hemodialysis	
	Calcitonin	Thyroid medullary carcinoma	
Other diseases contain amyloid deposits			
	Aβ	AD	Brain, senile plaque
	IAPP	Type 2 diabetes	Pancreas, islet amyloid
	Aβ	Down's syndrome (trisomy 21)	Brain, early-onset AD
	PrP	Transmissible spongiform encephalopathy	Cerebral amyloid deposits of PrP.

Abbreviations: FAP, familial amyloidotic polyneuropathy; SAA, serum amyloid A; IAPP, islet amyloid polypeptide; Aβ, amyloid β; AD, Alzheimer's disease.

evidence for the diagnosis of amyloid diseases without the presence of such remarkable deposits (Table 1). According to the different involved tissues and/or organs, as well as the preexisting of primary disease or not, localised/systemic amyloidosis and hereditary/acquired amyloidosis are recognized as the clinical classifications of amyloidoses (Pepys, 2006; Wechalekar et al., 2016). Furthermore, certain diseases such as Alzheimer's disease (AD), type 2 diabetes (T2D) and Transmissible spongiform encephalopathy (TSE) with the histopathological features of amyloid are also cited as examples of amyloidosis, but the amyloid plaques are not necessary for their development and/or progression (Cleary et al., 2005; Mallucci et al., 2003). By involved one type of tissue or organ, localised amyloidosis is much rarer than systemic amyloidosis, which make an enormous medical and social burdens worldwide (Mahmood et al., 2015).

2.2. Biochemical characteristics of amyloid

According to the 3D structural data of amyloid, three types of network structures including fibril meshwork, fibril bundle and amyloid star have been identified and are of functional relevance to host cells (Kollmer et al., 2016). Notably, different types soluble proteins can convert to insoluble amyloid fibrils with the common functional properties (Nelson et al., 2005). Insightful study has demonstrated that oligomers and fibrils contribute to extracellular aggregation directly associated with amyloidosis and amyloid-related disease, as well as acting as biological components such as cell growth support structure (Vauthey et al., 2002). Actually, although the molecular properties of many proteins in "amyloid stage" are in parallel with the development and/or progression of amyloid disease, such remarkable fibrils have beneficial effect on sequestering the toxic oligomers into nontoxic amyloid fibrils (Eisenberg and Jucker, 2012; Greenwald and Riek, 2010). Consequently, delicate balance among protein folding efficiency, misfolding, aggregation and degradation is responsible for maintaining the stability of functional proteins based on the complex regulatory system. Such regulatory system is known as proteostasis (protein homeostasis) network, and its collapse owes to aging, metabolic or environmental stress that related increased loss-of function diseases and gain-of toxic-function diseases (Powers et al., 2009). Given the central role of cellular proteostasis capacity, its imbalance may be at the core of amyloid diseases, which compromised to the presence of an everchanging proteome during development with terms of emerging new proteins and the accumulation of misfolded proteins upon aging (Balch et al., 2008).

2.3. Amyloidosis involves in inflammatory response

By now, effective management of amyloidosis depends upon identification of the formational mechanism of amyloid deposits involved in tissue damage and/or amyloidotic organ dysfunction (Gillmore and Hawkins, 2013). Outstandingly, increased expression of receptors for advanced glycation endproducts (RAGE) has been observed in systemic amyloidosis, activation of which triggers several immune responses (Yan et al., 2000; Durning et al., 2016). RAGE blockade prevents the initiation of autoimmune disease mediated by effector T cells, while accounts for the persistence of underlying inflammation (Durning et al., 2016). Furthermore, meaningful therapeutic interventions for amyloidosis has focused on the activation of inflammasome triggered by amyloid or misfolded protein aggregates, as well as the release of proinflammatory cytokine interleukin-1β (IL-1β) (Masters and O'Neill, 2011). Most profoundly, IL-1β and its receptor are essential for initiating Th17 immune response, which plays an important role in host defense (van de Veerdonk et al., 2011). Although Th17 cells benefit mucosal barrier function via secreting IL-17, IL-17F and IL-22, which are necessary for neutrophils recruitment, there is still a reciprocal relationship between Th17 and $CD4^+CD8^+FoxP3^+$ regulatory T cells (Tregs) balanced by the presence of IL-6 (Korn et al., 2009). According to this, IL-1 receptor expressed on T cells is critically required for the induction of experimental autoimmune encephalomyelitis (EAE), which unveils IL-1 receptor knockout resulting in selective defects in IL-17-producing T cells and accumulation of Tregs during the course of autoinflammatory response (Chung et al., 2009). Thus, immunotherapy for amyloidosis has shown great promise on the clinical outcomes, by which directly reducing amyloid deposition and alleviating the cascaded inflammatory responses (Lifshitz et al., 2012).