Cellular Immunology 289 (2014) 112–118

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Review

The impact of ageing on the intestinal epithelial barrier and immune system

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ARTICLE INFO

Article history:
Received 3 March 2014
Accepted 1 April 2014
Available online 12 April 2014

Keywords:
Ageing
Intestinal immunity
Intestinal epithelium
Intestinal barrier
Mucus
Antigen transport
Secretory IgA
Antigen presentation

ABSTRACT

The vast mucosal surface of the intestine is patrolled by a large number of lymphocytes forming the intestinal immune system. Like any other system in the body, this branch of the immune system is affected by ageing. Although our knowledge on the age-associated changes of the systemic immune system has improved over the past few years, our understanding of the mechanisms of senescence of both adaptive and innate immune system of the gastrointestinal (GI) tract is still largely incomplete. However, recent advances in the field have shown that the identification of the events underlying the ageing process in the gut may have important consequences on health and wellbeing far beyond the GI-tract. The aim of this review is to summarise the impact of ageing on the intestinal immune system, including the gut epithelium and other components of the intestinal barrier that maintain intestinal immune homeostasis and shape antigen-specific immune responses.

1. Introduction

Ageing is an ill-defined process involving changes in various body systems which converts a mature, fit person into an increasingly infirm one. With the passage of time, individuals show a lower degree of adaptation with consequent increase in mortality, due to increased incidence of cancer and infectious disease [1,2], as well as a decline of mental health, wellbeing and cognitive abilities [3–5]. Advancements in science and medicine, and improved living standards have led to an increase of the ageing population in Western societies. For example, latest figures show that 10 million people in the United Kingdom are over 65 years old, estimating that there will be 5½ million more elderly people in 20 years' time, with that number nearly doubling to around 19 million by 2050 [6]. This predicted increased life expectancy of the population has significant social and economic consequences. However, new research suggests that extending life span while reducing the prevalence of comorbities is a realistic goal, and that developing strategies to delay ageing can produce significant economic benefit, in excess of $7 trillion over a period of 50 years [7]. These data provide a compelling argument to increase our understanding of the ageing process, in order to improve the quality of life of an ever increasing segment of the population worldwide, and alleviate the economic burden associated to it.

One of the most important effects of the ageing process is a significant decline of the efficacy of both the adaptive and innate immune systems [8,9]; in particular, ageing has a profound influence on the intestinal immune system, and it would appear that age-associated alterations arise in the mucosal immune system of the GI-tract earlier than in systemic immune compartments [10]. Although our knowledge of the age-related changes of the systemic immune system has improved over the past few years, our understanding of the mechanisms of mucosal immunosenescence of the intestine is still largely incomplete. The aim of this review is to summarise the age-associated changes affecting the different stages of the gut immune response, from the early events occurring at the mucosal interface mediated by various components of the epithelial barrier, to the generation of antigen-specific immune responses.

2. Introduction to the intestinal immune system

It is generally accepted that the GI tract represents the largest immunologic organ in terms of numbers of lymphocytes and at any given time, the gut-associated lymphoid tissue (GALT) can

Abbreviations: GI, gastrointestinal tract; GALT, gut-associated lymphoid tissue; PP, Peyer's patch; M cell, microfold cell; FAE, follicle-associated epithelium; SED, subepithelial dome; LP, lamina propria; AMP, anti-microbial peptides; MLN, mesenteric lymph node; PRR, pathogen recognition receptor.

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http://dx.doi.org/10.1016/j.cellimm.2014.04.001
0008-8749/

accommodate nearly 70% of the total lymphocytes in the body [11]. Although this figure has been questioned by estimating the real number of lymphocytes in the gut to be closer to 5–20% of all lymphocytes [12], it is without doubt that the intestinal immune system copes daily with an antigen load that surpasses the one encountered by the systemic immune system during a lifetime. In the intestine, the immune system is present as isolated follicles scattered throughout the gut, or as aggregate follicles such as Peyer's patches (PPs) in the small intestine [13] (Fig. 1). These structures form the inductive sites of the gut immune system, the locations where antigen-specific immune responses have their origin. PPs essentially harbour all the immune competent cells necessary for induction of an antigen-specific B and T cell response; antigen presenting cells (APCs) such as dendritic cells (DCs) and macrophages, B cells, and $CD4^+$ T lymphocytes. The sub-epithelial dome (SED) area of PPs is the lymphoid microenvironment that is home to distinct subsets of DCs essential for T cell activation and regulation [14,15]. A unique adaptation of the specialised follicle-associated epithelium (FAE) of the PPs is the presence of antigen sampling microfold (M) cells which take up and transport antigens to the underlying immune machinery [16]. In contrast to the inductive sites, the effector sites consist of different anatomical compartments, such as the lamina propria (LP) populated with T cells, mostly $CD8^+$ T cells, IgA-producing plasma cells, and mononuclear cells such macrophages and DCs [17,18]. The intestinal immune system is separated from the external environment by a single cell layer that forms the intestinal epithelium whose importance in contributing to the intestinal immune homeostasis, elicitation of immune responses and shaping of the gut microbiota has become apparent over the past few years [19–21].

3. The intestinal epithelium in ageing

Although the main task of the epithelium overlying mucosal surfaces of the intestinal tract is the provision of an effective barrier to the vast majority of macromolecules and microorganisms present in the intestinal lumen, it has become evident in the past few years that the epithelial layer is much more than a mere physical barrier. Indeed, intestinal epithelial cells (IECs) engage in a dynamic cross-talk with the intestinal immune system [22,23] that helps to achieve the task of discriminating between invasive pathogenic organisms and harmless antigens, such as food, and the large number of microbes that make up the intestinal microbiota. In spite of its critical role, so far the effect of ageing on epithelial cell immune function has not been addressed in detail. The intestinal epithelium is a rapidly renewing tissue which sheds significant numbers of cells each day. It is organised into self-renewing 'crypts', with colonic stem cells at the crypt-base dividing asymmetrically to self-renew and form progenitor cells [24]. The progeny proliferate, migrate, differentiate and undergo shedding from the surface of the epithelium. Perpetual tissue renewal should

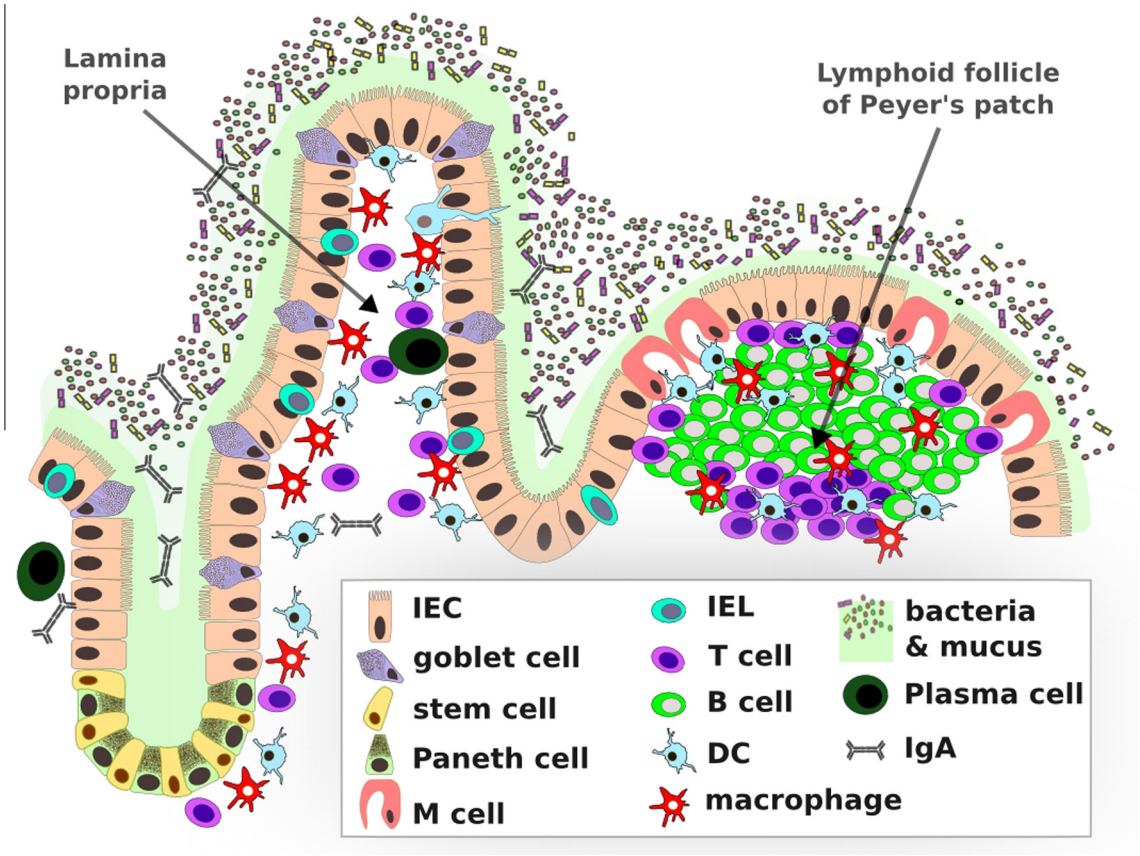

Fig. 1. Three-way cross talk in the gut. Schematic illustration of the structure and various components of the intestinal immune system. The microbes, intestinal epithelium and the underlying immune system closely work together to establish and maintaining intestinal immune homeostasis. The presence of PRRs on intestinal epithelial cells and antigen transport across follicle-associated epithelium (FAE) M cells allow the gut immune system to constantly survey the intestinal luminal contents and to generate rapid and effective immune response in the presence of pathogenic organisms. After the initial interaction within lymphoid follicles of the Peyer's patches, the inductive sites of mucosal immunity, antigen-specific B and T cells recirculate to the lamina propria of distant mucosal effector sites. The surface of the epithelium is covered by a mucus layer produced mainly by goblet cells that contains large amount of SIgA the main role of which is to prevent microbes from crossing the epithelial barrier. Ageing has a detrimental effect on function of many components (see summary in Table 1) of the intestinal immune system the ultimately lead to a reduce ability to mount effective immune responses and to control the local, and possibly systemic, inflammatory status.