Seminars in Immunology 36 (2018) 31–44

Contents lists available at ScienceDirect

Seminars in Immunology

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

Review

The immunological functions of the Appendix: An example of redundancy?

Mathilde J.H. Girard-Madoux[a,*], Mercedes Gomez de Agüero[b], Stephanie C. Ganal-Vonarburg[b], Catherine Mooser[b], Gabrielle T. Belz[c,d], Andrew J. Macpherson[b], Eric Vivier[e,f,g]

[a] Centre d'Immunologie de Marseille-Luminy, Aix-Marseille Université, INSERM, CNRS, Marseille, France
[b] Maurice Müller Laboratories (Department for Biomedical Research), Universitätsklinik für Viszerale Chirurgie und Medizin Inselspital, Murtenstrasse 35, University of Bern, 3010 Bern, Switzerland
[c] Walter and Eliza Hall Institute of Medical Research, Parkville, Melbourne 3052 Australia
[d] Department of Medical Biology, University of Melbourne,Parkville, Melbourne, 3010, Australia
[e] Innate Pharma Research Labs, Innate Pharma, Marseille
[f] Aix Marseille Univ, CNRS, INSERM, Centre d'Immunologie de Marseille-Luminy, Marseille, France
[g] Service d'Immunologie, Marseille Immunopole, Hôpital de la Timone, Assistance Publique des Hôpitaux de Marseille

ARTICLE INFO

Keywords:
Appendix
Caecal patch
Microbiota
Secondary lymphoid organ
Redundancy

ABSTRACT

Biological redundancy ensures robustness in living organisms at several levels, from genes to organs. In this review, we explore the concept of redundancy and robustness through an analysis of the caecal appendix, an organ that is often considered to be a redundant remnant of evolution. However, phylogenic data show that the Appendix was selected during evolution and is unlikely to disappear once it appeared. In humans, it is highly conserved and malformations are extremely rare, suggesting a role for that structure. The Appendix could perform a dual role. First, it is a concentrate of lymphoid tissue resembling Peyer's patches and is the primary site for immunoglobulin A production which is crucial to regulate the density and quality of the intestinal flora. Second, given its shape and position, the Appendix could be a unique niche for commensal bacteria in the body. It is extremely rich in biofilms that continuously shed bacteria into the intestinal lumen. The Appendix contains a microbiota as diverse as that found in the colon and could replenish the large intestine with healthy flora after a diarrhea episode. In conditions of modern medicine hygiene, and people live healthy without their appendix. However, several reports suggest that the effects of appendectomy could be subtler and associated with the development of inflammatory conditions such as inflammatory bowel disease (IBD), heart disease but also in less expected disorders such as Parkinson's disease. Lack of an Appendix also predicts a worsen outcome for recurrent Clostridium difficile infection, which is the first nosocomial infection in hospitals. Here, we review the literature and in combination with our own data, we suggest that the Appendix might be redundant in its immunological function but unique as a reservoir of microbiota.

1. Introduction

Organisms are continuously exposed to internal and external fluctuations and disturbances, such as temperature variations, changes in diet, trauma, infectious diseases and cancers. Robustness, also in an organism, is the ability to absorb and withstand disturbances and crises, and this concept encompasses that of reliability. Redundancy involves back-up systems, making it possible to maintain core functions in the event of disturbances. Redundancy and compensatory mechanisms are required during both homeostasis and activation of the immune system. Redundancy ensures robustness, which underlies the persistence and function of the organism [1].

Genetically, robustness is ensured by gene redundancy, which reduces the effect of genetic mutations in one copy of a gene [2]. The genetic code is itself optimized such that most point mutations lead to the incorporation of similar amino acids into the protein [3].

Abbreviations: α-syn, alpha-synuclein; AA, appendicitis/appendectomy; CCR, C-C chemokine receptor; CD, Crohn's disease; CXCR C-X-C, chemokine receptor; DSS, dextran sulfate sodium; GALT, gastrointestinal lymphoid tissue; IBD, inflammatory bowel disease; Ig, immunoglobulin; IL, interleukin; ILC, innate lymphoid cell; ILF, isolated lymphoid follicle; IFN, interferon; Lti, lymphoid tissue inducer cell; PD, parkinson's disease; PP, peyer's patches; SCID, severe combined immunodeficient; SILT, solitary intestinal lymphoid tissue; TCR, T cell receptor; Th, T helper; UC, ulcerative colitis

* Corresponding author at: Centre d'immunologie Marseille-Luminy, Parc Scientifique et Technologique de Luminy, Case 906, F 13288 Marseille, Cedex 09, France.
E-mail addresses: girard@ciml.univ-mrs.fr (M.J.H. Girard-Madoux), mercedes.gomez@dbmr.unibe.ch (M. Gomez de Agüero), stephanie.ganal@dbmr.unibe.ch (S.C. Ganal-Vonarburg), catherine.mooser@dbmr.unibe.ch (C. Mooser), belz@wehi.edu.au (G.T. Belz), Andrew.macpherson@dbmr.unibe.ch (A.J. Macpherson), vivier@ciml.univ-mrs.fr (E. Vivier).

https://doi.org/10.1016/j.smim.2018.02.005
Received 2 January 2018; Accepted 16 February 2018
Available online 02 March 2018

Robustness at protein level is ensured by the ability of many sequences to form very similar structural folds [4]. At the cellular level, innate lymphoid cell (ILC) deficiency was recently reported to be clinically silent in conditions of modern medicine and hygiene provided that functional T and B cells are present [5]. Immune compensation generally provides a back-up system to fight pathogens, but it may lead to an overactivation of pathways that is harmful to the individual [6]. There is also redundancy at organ level, as for instance humans have two kidneys, which perform the same function, and it is possible to live in full health with only one kidney.

It was long thought that the Appendix was just a remnant of the caecum, an intestinal structure in which plants are fermented, and that modern humans inherited the Appendix from an ancestor who ate leaves. However immunological studies and phylogenic data have suggested that, far from being redundant, the Appendix may have adapted to have a specific function of its own. The role of the Appendix has always been controversial, fueling the debate between evolutionists and advocates of the teleological school in the late 19th century [7,8]. However, the high density of lymphoid tissue in the vermiform Appendix led to suggestions, as far as in 1900 that the Appendix might be involved in the immune responses [9]. Furthermore, given its shape and position, the Appendix could shelter symbiotic gut microbes against the damage due to gastrointestinal infections. Both these functions would probably be subject to selection, accounting for the persistence of the Appendix over time. The Appendix may, therefore, have a unique function rather than being a redundant organ. We will review here the current knowledge on the Appendix and provide new data to enlighten the discussion on its immunological function.

2. The appendix

2.1. Anatomy

The Appendix is a narrow tube-shaped sac extruding from the wall of the posteromedial caecum. In humans it is often referred to as the 'vermiform appendix', from the Latin vermiforma, meaning 'worm-shaped'. The development of the caecum and Appendix is closely linked to that of the midgut, all three structures being irrigated by the superior mesenteric artery. In humans, the vermiform Appendix becomes visible at eight weeks of gestation and, by 14–15 weeks, the lymphoid tissue begins to develop within it [10]. In adults, the vermiform Appendix is 5–35 cm long, with a mean length of 9 cm. Its shape varies between individuals and it is found in five different positions, the retrocaecal position being the most common [11,12]. Several Appendix malformations have been identified, including the congenital absence of an appendix (agenesis), which is extremely rare and often misdiagnosed due to confusion with hypoplasia or intramural positions [13,14]. Other malformations include duplication [15], a horseshoe-shaped Appendix [16,17], and atresia, the closure of the opening of the Appendix into the caecum, this malformation preventing flow between the appendiceal and caecal lumina [18]. These developmental abnormalities are extremely rare and were last classified in 2016 [16]. A survey of human appendices covering 50,000 specimens identified only two cases of duplication and four of agenesis [19]. The Appendix is, therefore, highly conserved in the human population, consistent with an important role for this structure. By contrast, wisdom teeth, for example, are tending to disappear in the population with changes to our diet that have rendered these third molars obsolete [20].

2.2. Evolution

The assumption that the Appendix had been lost over time in many species has proved false. Indeed, it has existed for more than 80 million years in the mammal clade and has reappeared significantly more times than it has disappeared, suggesting a real biological function [21,22]. The Appendix is often considered to be a vestigial organ, a shrunken remnant of the caecum that ceased to be required when the human diet diversified. The caecum is present in all herbivores. It serves as a site of fermentation, facilitating cellulose digestion. However, there is no correlation between caecum size and the presence and size of the appendix. Indeed, the association between a decrease in caecum size and the appearance of an appendiceal structure is exceptional, and certainly not the rule in the evolution of the Appendix [23]. Contrary to the dietary hypothesis of caecal Appendix evolution, recent studies have shown that there is no correlation between the presence of the appendix, its size and morphology, and dietary habits [21,22]. By contrast, a significant correlation was found between the presence of an Appendix and both caecal apex thickness and caecal morphology (the presence of an Appendix is mostly associated with a tapering or spiral caecum) [22]. Inventory studies of the presence or absence of an Appendix or similar structure in more than 500 mammal species showed that the Appendix has appeared on at least 30 independent occasions in mammalian lineages, whereas it has been lost no more than 12 times. The Appendix was also found to be unlikely to disappear once it had appeared [22]. These observations strongly suggest that the Appendix has been subjected to positive selection during evolution. However, appendiceal structures differ considerably between taxonomic groups, suggesting a complex and diverse pattern of evolution for this structure [22]. Phylogenic and comparative anatomy studies in mammals have shown that the Appendix is present in primates, lagomorphs (such as rabbits), a few rodents and some marsupials, in which it has appeared on at least three independent occasions [21,22]. The rabbit is the only commonly used laboratory animal to possess a vermiform appendix. This structure is absent in rats, guinea pigs, pigs, cats and dogs, although all these animals have a caecum with lymphoid tissue at its apex [24]. In mice, this pouch of lymphoid tissue is called the caecal patch and it resembles Peyer's patches (PPs). Fish and amphibians have no caecum and no lymphoid tissue at the corresponding position in the intestine, but birds do have lymphoid tissue at this site [9]. Conversely, within marsupials, the wombat has a long Appendix but no caecum [25]. Remarkably, in all animals possessing a caecum, this structure contains large amounts of lymphoid tissue, aggregated into distinct masses or diffusely spread along the entire length of the caecum [9,22]. These two characters are significantly correlated in mammalian evolution [22]. In all species, the caecum/appendix clearly contains excess lymphoid tissue relative to the rest of the intestine. In some species that ferment their food in the foregut, the caecum has shrunk with evolution and lost its digestive function, but it has retained its immunological function [21]. In primates, an Appendix is present in macaques, orangutans, chimpanzees and gorillas, but with different morphological features in different species. The Appendix of the macaque is more rudimentary and less vermiform than that of the gorilla, which is similar to that of humans [26]. The more developed Appendix of higher primates, culminating in the vermiform Appendix in gorillas and humans, further suggests that the Appendix may perform a particular function rather than being a degenerate structure.

3. The Appendix consists of dense lymphoid tissue

The appendiceal wall has a composition similar to that of the colon wall: mucosa, submucosa, muscularis externa and serosa. However, the Appendix also contains dense lymphoid tissue with a lymph node-like structure, with B cells forming follicles and T cells in the interfollicular region [27,28].

3.1. Development of appendiceal lymphoid tissue

Comparative anatomy studies have revealed morphological and qualitative similarities between the appendices of humans and rabbits and the bursa of Fabricius in birds, a specialized organ dedicated to hematopoiesis present in the cloaca. The Appendix was initially studied in rabbits. The rabbit Appendix resembles the human vermiform