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Review

The inflammatory status of the elderly: The intestinal contribution

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ABSTRACT

A common finding in the elderly population is a chronic subclinical inflammatory status that coexists with immune dysfunction. These interconnected processes are of sufficient magnitude to impact health and survival time. In this review we discuss the different signals that may stimulate the inflammatory process in the aging population as well as the molecular and cellular components that can participate in the initiation, the modulation or termination of the said process. A special interest has been devoted to the intestine as a source of signals that can amplify local and systemic inflammation. Sentinel cells in the splanchnic area are normally exposed to more than one stimulus at a given time. In the intestine of the elderly, endogenous molecules produced by the cellular aging process and stress as well as exogenous evolutionarily conserved molecules from bacteria, are integrated into a network of receptors and molecular signalling pathways that result in chronic inflammatory activation. It is thus possible that nutritional interventions which modify the intestinal ecology can diminish the pro-inflammatory effects of the microbiota and thereby reinforce the mucosal barrier or modulate the cellular activation pathways.

Contents

1. Introduction: the inflammatory response

The inflammatory response is an adaptive, coordinated process, the main functions of which are to clear infectious agents from the body, to get rid of tissues damaged by physical or chemical injury and finally, to return the tissue to functional homeostasis. More recently, it has also been postulated that a milder inflammatory response is engaged whenever tissue malfunctioning is detected [1]. Thus, depending on their microenvironment, host tissues are in a basal homeostatic state, stressed or undergoing apoptosis and necrosis.

Tissue sentinel cells such as macrophages, dendritic cells (DC) and mast cells, normally maintain homeostasis and promote an adequate adaptive response to challenge [2]. A change in the internal environment induces a cellular stress response that is normally handled by the resident sentinel cells but, if needed, these cells produce chemokines that recruit the help of more inflammatory cells [3]. In the healthy intestine, tissue derived signals then restore

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homeostasis and functionality [2]. Intrinsic to the efficacy of the inflammatory reaction is the ability to mount a rapid response that is appropriate to the particular type of injury, is self-limiting and involves minimal damage to host tissues [4]. However, all of these processes involve an enormous expenditure of metabolic energy, particularly following severe injury when the damage to host tissues requires repair. It is not surprising therefore that dysregulation of the inflammatory response has been strongly associated with the development of frailty in older persons [5,6].

At the onset of the inflammatory process, a signal or inducer of inflammation enters in contact with cells of the host's innate immune system. An accepted paradigm in innate immunity is that there are two major types of activation signals: (a) infectious non-self and, (b) endogenous danger signals [7] that are released from their intracellular environment during cell stress and/or are molecules that are modified by tissue injury. However, more recently, tissular dysfunction has also been proposed to initiate an inflammatory response, albeit of milder intensity [2]. Both exogenous and endogenous danger signals are detected by a limited repertoire of invariant receptors or sensors called pattern recognition receptors (PRRs) [8], which are expressed on the sentinel cells of the innate immune system. The signals can act in both extracellular and intracellular compartments and, depending on the magnitude of the signalling events that are initiated, can lead to an innate response which (1) activates the inflammatory cascade; (2) activates the adaptive immune response and/or (3) restores tissue homeostasis. This review will discuss signals that are delivered to the intestinal mucosa, alter mucosal homeostasis and modify the systemic inflammatory response and, as such, may contribute to the aging process.

2. Sensing the infectious non-self

The innate immune system recognizes conserved microbial components called pathogen-associated molecular patterns (PAMPs). Different classes of PRR such as toll-like receptors (TLRs), nucleotide binding oligomerization domain (Nod) receptors (NLRs), and retinoid acid-inducible gene (RIG)-like receptors (RLRs) recognize specific PAMPs in different cellular compartments. TLR-4 recognition of the lipopolysaccharide (LPS) from Gram-negative bacteria is one of the most characterized interactions between PAMPs and host PRR. TLRs are expressed on macrophages, DC, neutrophils, mast cells and epithelial cells and are involved in the recognition of bacteria, viruses, and fungi at the cell surface or in endosomes [9]. Upon ligand interaction, they activate the transcription factors NF-κB and IFN-regulatory factor (IRF) [10], the nuclear translocation of which results in activation of pro-inflammatory genes (TNF-α, IL-1).

NLRs and RLRs sense microbes in the cell cytosol and are particularly important in the recognition of intracellular pathogens. NLR family members Nod 1 and Nod 2 sense respectively γ-D-glutamyl-*meso*diaminopimelic acid that is found in the peptidoglycan (PGN) of most Gram-negative bacteria and certain Gram-positive bacteria [11] or muramyl dipeptide (MDP), a component of nearly all types of PGN. In both cases, ligand recognition leads to NF-κB-mediated signalling [12]. NALPs (NACHT-LRR-PYD-containing proteins), more recently identified members of the NLR family, recognize intracellular bacterial RNA, toxins and flagellin [13,14]. Together with the adaptor molecule ASC (Associated Speck-like protein containing a CARD domain) they form part of a multiprotein cytosolic complex, known as the inflammasome which, upon ligand recognition, activates caspase-1 and the subsequent processing and maturation of the pro-inflammatory cytokines interleukin 1β (IL-1β) and IL-18 [15]. Indeed, some pathogens inject virulence factors directly into the cytosol of the host cell and activate caspase-1 [13]. Finally, the RLR homologues, RIG-I and melanoma differentiation-associated protein-5 (MDA-5), recognize and respond to viral RNA and microbial and host DNA in the cytosol [11,16,17].

3. Sensing non-self in the intestinal mucosa: host–microbiota interactions

Throughout the intestinal tract, at sites of bacterial colonization, there is an enormous quantity and diversity of microbial components capable of inducing inflammation and yet, tissue homeostasis is maintained. Certainly, the mucous layer and epithelial barrier integrity prevent an overwhelming onslaught of bacterial products from reaching the internal milieu. However, a "physiological" translocation of bacteria and their products, as well immune sampling of intestinal contents, occurs all the time [18]. Furthermore, certain members of the gut microbiota, although in the minority, are potentially pathogenic or true pathogens and represent a real threat to the host. Clearly, the normal intestinal immune system has evolved tightly regulated control mechanisms that allow it to differentiate between symbiotic and pathogenic organisms and ensure immunological tolerance to the normal microbiota and a protective defence against pathogens.

Non-pathogenic bacteria, perhaps by limited TLR stimulation, promote a mild transient innate activation that contributes to the physiological, low-level of inflammation in the healthy intestine. In contrast, true pathogens induce a rapid and more aggressive response that is initiated by microbial "danger signals" and tissue damage or is due to the pathogen's direct interaction with intracellular PRR, such as NALPs or inflammasome components. Taken together, the host immune response can be considered as a two-tiered process which, in a first instance, involves the activation of pro-inflammatory genes by most bacteria, pathogenic or not. Thereafter, the bacteria invoke a second clusters of genes, the nature of which is determined by the type of PAMP, the specific virulence traits of the organism and/or its interaction with the inflammasome [19].

It is now known that the innate and adaptive immune activation induced by the microbiota prevent other inflammatory responses and induce cytoprotective responses of the intestinal epithelium that are critical for intestinal homeostasis [20–23]. This is achieved, at least in part, by a low expression of PRRs (TLR-2 and -4) on intestinal epithelial cells (IEC) and, as such, limited interaction with bacterial ligands at the apical surface [24]. It results in the activation of the peroxisome proliferator-activated receptor γ that limits pro-inflammatory cell signalling by potentially pathogenic components of the microbiota [21]. Moreover, it initiates limited gene activation via NF-κB and promotes epithelial integrity through the production of cytoprotective molecules such as heat shock proteins [23].

The intestinal lamina propria and immune tissues underlying the intestinal epithelium, are home to an extensive network of innate immune cells, including macrophages and conventional $CD11c^+$ DC with antigen-presenting function. The cells shape the course of the immune response and prevent destructive inflammatory responses to commensals. More specifically, DC transport antigens and commensal bacteria to the mesenteric lymph nodes (MLN) where they interact with B and T cells. This results in production of secretory IgA and the development of IL-10 and TGF-β expressing T_{Reg} cells which maintain a non-inflammatory state in the intestine [25].

4. Sensing endogenous danger signals

Endogenous danger signals are generated during trauma, ischemia, ischemia-reperfusion, chemical injury, burns and to