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Review

Immunity and Inflammation: From Jekyll to Hyde

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ABSTRACT

The immune system is the defense system of the host that protects it from foreign pathogens. Inflammation is one of the key processes that alert the immune system but when loss of regulation occurs, a long-term chronic inflammation settles and is likely to be detrimental to the host. Most age-related diseases are linked to a dis-equilibrium of circulating inflammatory molecules. We could use the analogy of "Dr Jekyll' representing the expected inflammation and immune response in general and the "Mr. Hyde" effect represented by the other face of inflammation, when it is dysregulated. This review aims to cover how immunity, inflammation and persistent infection are associated and some aspects that future studies should look into such as tissue-specific immunity and interventions. Having this knowledge will enable us to prevent inflammation to lose its regulatory network, which could potentially increase the health-span and a better quality of life for the growing elderly population.

1. Immunity and inflammation

The immune system is the defense system in living organisms that protects the host from foreign pathogens (i.e. bacteria and viruses). The immune system can generally be classified into two different arms, which are the Innate and the Adaptive immune system. While the innate immune system responds quickly but non-specifically, the adaptive immune system has the specificity (T cell receptor, B cell receptor) and the "memory" capacity against previous infections. This enables it to protect the host during a primary infection and provide with a stronger and better adapted response following secondary infection by the same pathogen (Medzhitov & Janeway, 1997). However, recent studies have also shown that innate immunity could display "memory skills" or rather that it could adapt to the series of challenges, leading to a switch in their metabolic (and epigenetic) features which is also known as trained immunity (Netea et al., 2016). This new concept will probably change the way we look at the immune system and how inflammation is regulated.

One of the first cues during an infection is inflammation, which alerts and recruits the surrounding immune cells to the localized area of infection. Immune cells such as macrophages (Fujiwara & Kobayashi, 2005) and dendritic cells (DCs) (Hespel & Moser, 2012) releases pro-inflammatory cytokines (e.g. TNF-α, IFN-γ) upon ligation of their pattern recognition receptors (PRRs) with pathogen-associated molecular patterns (PAMPs) present on the bacteria surfaces or viruses' DNA/RNA (Medzhitov, 2002). This process will then lead to the release of other chemicals that induce vasodilation of the blood vessels (Ley et al., 2007), which increases the recruitment rate of other innate immune cells such as neutrophils (Mantovani et al., 2011) and monocytes (Shi & Pamer, 2011) to the inflamed site. At the inflamed site, these newly recruited immune cells will then secrete chemokines to recruit other immune cells to aid in the fight of the infection and these series of events together form the Inflammatory Response. Inflammation is a physiological process meant to alert the immune system of pathogen presence, tissue injury or other aggressions. It is a necessary process (the "Dr. Jekyll") to activate mechanisms leading to control of pathogens, resolution of pathogen/injury-associated collateral damages and clearance of damaged tissues. The issues that may arise following inflammation are the loss of control (the "Hyde" effect), sustained low grade inflammation or lack of amplitude in immunosuppressed individuals. Thus, inflammation is a necessary process that requires a tight regulation and the regulatory functions of the immune system are important to control infection and resolution of inflammation. This avoids hampering of the immune responses and reduces the risks of diseases onset (Fig. 1).

2. Acute and chronic inflammation

Inflammation occurs in two forms: as an acute (short-term) or chronic (long-term) process (Feghali & Wright, 1997). While most

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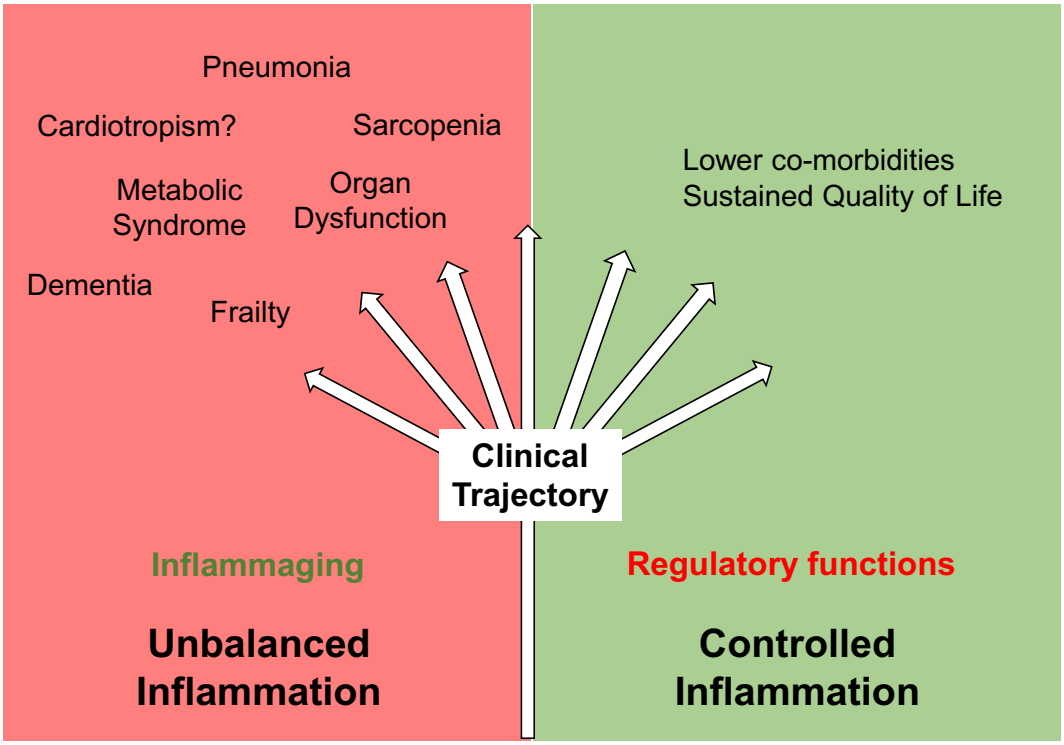

Fig. 1. Inflammation as a driving force influencing clinical trajectories during aging.

infections will trigger only acute inflammation and will end upon resolution of the infection, some infections such as HIV (Human Immunodeficiency Virus) (Fülöp et al., 2013) can cause persistent infection, which is associated with chronic inflammation and higher susceptibility to diseases. It is often stated that HIV induces an accelerated aging of the immune system which is accompanied by other clinical outcomes such as frailty (Fulop et al., 2016). Other infections such as CMV (Cytomegalovirus) have also been shown to exert a pressure on the immune system (Koch et al., 2007; Solana et al., 2012). As such infection is not fully resolved by the immune system, the concern is the reactivation of the virus when the host immune system is showing signs of "fatigue". This generally happens during cases such as chemo-therapy or organ-graft transplant whereby the patient immune system is suppressed and this issue will persist until vaccines become available for these persistent infections. CMV was shown to be particularly problematic especially as it induces clonal expansion and filling of the immunological space with CMV-specific T cells. Recent work has suggested that not only known persistent virus but also acute infections could lead to chronic immune response and associated inflammation (Da Fonseca et al., 2015). Despite the clearance of *Yersinia pseudotuberculosis*, inflammation persists and influences various processes, compromising the overall immune functions. This highlights the importance of tissue/immunity interaction in the maintenance of immune function and also suggests that tissue immunity should be better characterized as local inflammation may be a major source of peripheral inflammation observed in various clinical settings. The fact *Helicobacter pylori* infection, even after clearance with antibiotics, is associated with persistent inflammation and increased prevalence of stomach cancer is a good example of local inflammation persisting without the presence of the pathogen and the role of inflammation in cancer (Coussens & Werb, 2002).

3. Chronic inflammation, age-related disease and senescent cells

Though inflammation is important in resolving infections efficiently, chronic inflammation is detrimental to the host's health. Chronic inflammation has been associated with many diseases such as coronary heart disease, rheumatoid arthritis and cancer (Coussens & Werb, 2002; Álvarez et al., 2007; Baecklund et al., 2006; Hansson, 2005). Studies have shown that the plasma levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, IL-6 and C-Reactive Protein (CRP) are often higher in the elderly individuals when compared to young individuals (Franceschi & Campisi, 2014; Fülöp et al., 2016; Gabay, 2006). This could explain why there are higher incidences of these diseases in the elderly individuals compared to the young individuals.

One factor that could contribute to the higher level of pro-inflammatory cytokines in the elderly is the increased number of senescent cells in the host. As cells proliferate and differentiate, they will eventually reach the stage of replicative senescence, otherwise known as the Hayflick Limit (Ruben & Biology, 2000), whereby they have an impaired proliferative capacity. When cells reach this stage, they adopt a phenotype known as the Senescence Associated Secretory Phenotype (SASP),which is a concept established on fibroblasts. SASP fibroblasts have been shown to be involved in wound healing and tissue re-modeling (Coppé et al., 2010; Jun & Lau, 2010) but they have also been shown to secrete low level of pro-inflammatory cytokines into the environment. Besides fibroblasts, immune cells such as the T lymphocytes are also affected similarly with age. With age, the human thymus involutes, which causes a decrease in the output of naïve T cells. Coupled to that, elderly individuals have a longer infection history and this results in an increase in the proportion of highly differentiated T cells many of which display a replicative senescence profile (Kared et al., 2014). This phenomenon of T cell senescence is enhanced with persistent infections such as CMV and HIV (Fülöp et al., 2013; Vallejo et al., 2004) and there is a parallel between senescence of T cells and fibroblasts whereby they lose their proliferative capacity but are able to secrete low amount of pro-inflammatory cytokines even when they are not stimulated (Kared et al., 2014). Besides senescent cells, other factors such as visceral fats and microbiota changes in the elderly individuals have also been associated with higher level of systemic chronic inflammation (Fontana et al., 2007; Magrone & Jirillo, 2013;