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Presidential Address

Stress-evoked sterile inflammation, danger associated molecular patterns (DAMPs), microbial associated molecular patterns (MAMPs) and the inflammasome

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ABSTRACT

Since the inception of the field of psychoneuroimmunolology research, there has been an appreciation that the physiological response to stressors includes modulation of immune function. Investigators initially focused on the effect of stress on cellular migration and immunosuppression and the resultant decreases in tumor surveillance, anti-viral T cell immunity and antigen-specific antibody responses. More recently, it has become clear that exposure to stressors also potentiate innate immune processes. Stressor exposure, for example, can change the activation status of myeloid lineage cells such as monocytes, macrophages, neutrophils, and microglia, leading to a primed state. In addition, stressor exposure increases the synthesis and release of a vast cadre' of inflammatory proteins both in the blood and within tissues (i.e., spleen, liver, adipose, vasculature and brain). The mechanisms for stress-evoked innate immune 'arousal' remain unknown. The goals of this presidential address are the following: (1) offer a personalized, brief overview of stress and immunity with a focus on 'aroused' innate immunity; (2) describe sterile inflammatory processes and the role of the inflammasome; and (3) suggest that these same processes likely contribute to primed myeloid cells and inflammatory protein responses (systemic and tissue) produced by stress in the absence of pathogens.

1. Introduction: A brief history of stress and immunity

1.1. Stress and immunosuppression

There is strong evidence in both the animal and human literatures that exposure to acute and chronic stressors impact mental and physical health. Stressor exposure, for example, can exacerbate the symptoms of many diseases including anxiety (Vinkers et al., 2008), depression (Charney and Manji, 2004), multiple sclerosis (Mei-Tal et al., 1970), irritable bowl syndrome (Mayer et al., 2001), diabetes (Black, 2006), obesity (Bose et al., 2009) and cardiovascular disease (Hartel, 1987; Pickering, 2001). In addition, intense or exhaustive stress can increase vulnerability to illness after exposure to infectious pathogens (Kiecolt-Glaser et al., 1996; Pedersen et al., 2010) and increase cancer metastasis (Dhabhar et al., 2012; Moreno-Smith et al., 2010).

1.2. Stress and immune potentiation

These observations in the human literature fueled mechanistic animal stress research that initially relied on crude *in vitro* measures of T and B cell mitogen-stimulated proliferation, but then rapidly progressed to better *in vivo* measures of specific immunity. For example, using a well-established animal model of stress (uncontrollable tailshock) that had been previously documented to produce anxiety/depressive-like behaviors and cognitive deficits (Maier, 1991, 1984; Maier and Watkins, 2005; Strong et al., 2011, 2009), we published several studies documenting a long-term suppression in the generation of KLH specific, T-cell dependent, antibody responses (Fleshner et al., 1996, 2001, 1998; Gazda et al., 2003; Laudenslager et al., 1988). There is also a rich literature demonstrating that exposure to intense acute stressors or chronic/repeated stressors, suppresses specific anti-viral host defense (Kusnecov et al., 1992; Padgett et al., 1998; Sheridan et al., 1998, 2000) and anti-tumor immunity (Ben-Eliyahu et al., 2007, 2000), making organisms vulnerable to pathogen-evoked disease and cancer.

Fig. 1A depicts the results of a PubMed search of the literature using the key words immunosuppression and stress. As early as the 1970s and 1980s, many papers were published on this topic. In addition there is a gradual increase in the total number publications through the 2000s (i.e., 2000–2009). Although stress and immunosuppression was the initial dogma, work was beginning to appear in the literature that stressor exposure could also increase some aspects of specific immunity especially if the antigenic challenge involves the dermis (Blecha et al., 1982a, 1982b; Dhabhar and McEwen, 1996; Dhabhar and Viswanathan, 2005; Viswanathan et al., 2005). Evidence was also rapidly mounting that stress could

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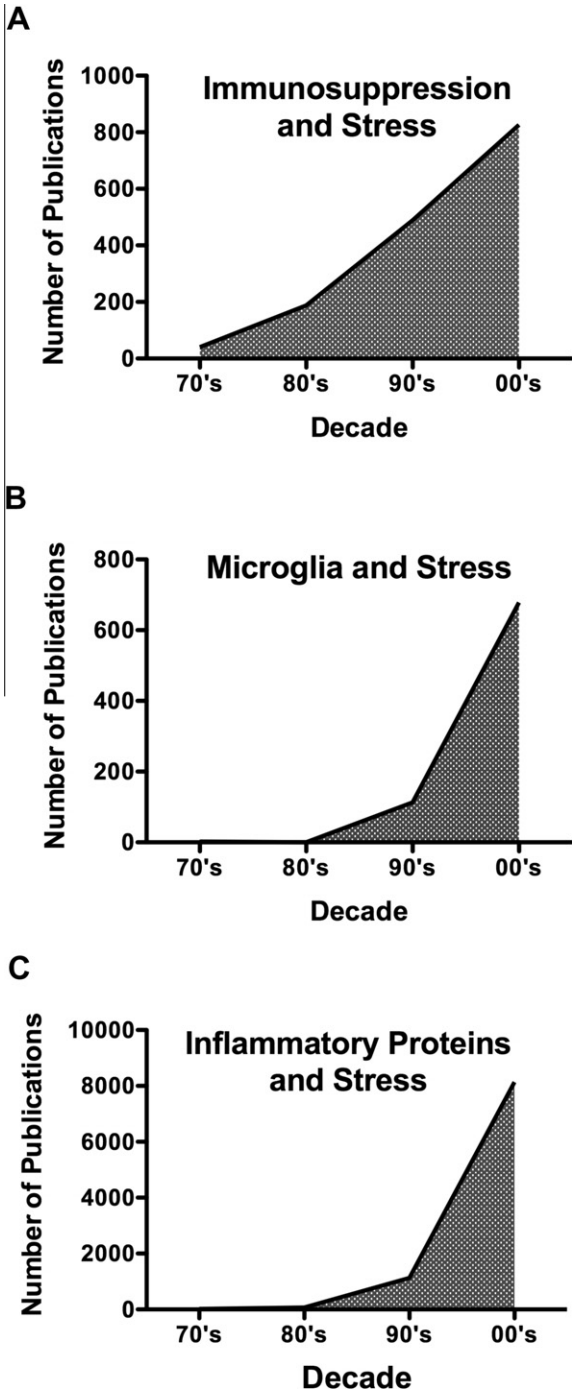

Fig. 1. (A) Depicts the results of a PubMed search of the literature using the key words immunosuppression and stress. As early as the 70s and 80s, many papers were published on this topic. In addition there is a gradual increase in the total number publications through the 2000s (i.e., 2000–2009). (B) Depicts the results of a PubMed search of the literature using the key words microglia and stress. Prior to 1990 there were only 2 publications, one in 1975 and one in 1976. Since 1990 there is a rapid increase in work in this area, with a large jump in the number of papers published in the 10–12 years. (C) Depicts the results of a PubMed search of the literature using the key words inflammatory proteins and stress. The upturn in publication rate of papers investigating the impact of stressor on inflammatory proteins mirrors the sharp increase in publication rate focusing on stress and microglia.

potentiate innate immunity (Campisi et al., 2002, 2003, 2012; Deak et al., 1999). In the 1990s, for example, it was reported that the exposure to the same stressor could both potentiate innate immunity (i.e., bactericidal, inflammatory proteins, complement, macrophage priming) and suppress antigen-specific antibody responses (Fleshner et al., 1998).

The priming effects of stressor exposure on innate immunity were initially revealed in peripheral myeloid cells including monocytes from the blood and macrophages (Broung-Holub et al., 1998). The functional consequences of stress-evoked peripheral myeloid cell priming include faster bacterial killing and phagocytosis resulting in faster bacterial inflammation resolution (Allen et al., 2012; Bailey et al., 2007; Campisi et al., 2002; Deak et al., 1999; Leem et al., 2000), and exaggerated inflammatory cytokine responses and febrile responses to subsequent low dose lipopolysaccharide (LPS) (Johnson et al., 2002a, 2002b, 2002c). The idea that was emerging is that stress-evoked increases in these innate immune responses could be an adaptive feature of the acute stress response, such that if a gazelle running from the lion and were wounded during the attack, it would be better equipped to utilize innate immune processes for recovery, thus improving its chances for survival (Fleshner et al., 2006). This scenario is quite reasonable in a healthy organism exposed to an acute stressor. If, however, the stressor and hence the elevated inflammatory proteins or primed myeloid cell function persists, or the organism suffers from an inflammatory disease, than pathology may ensue (Fleshner et al., 2007).

More recently, research has focused on stress-evoked priming of brain myeloid cells, i.e., microglia. This area of inquiry has rapidly increased with evidence of stress-evoked microglia arousal occurring following a vast array of stressors including experimental stressors (e.g., tailshock (Frank et al., 2012), social defeat (Wohleb et al., 2011), prenatal stress (Diz-Chaves et al., 2012)), physiological stressors (e.g., aging (Morgan et al., 1999; Wynne et al., 2009), high fat diet (Grayson et al., 2010), radiation (Schnegg et al., 2012)), and alcohol (Cooper et al., 2012; Ehrlich et al., 2012; McClain et al., 2011). Fig. 1B depicts the results of a PubMed search of the literature using the key words microglia and stress. Prior to 1990 there were only two publications, one in 1975 and one in 1976. Since 1990 there is a rapid increase in work in this area, with a large jump in the number of papers published in past the 10–12 years. The consequences of primed microglia in central nervous system are many and include pathological pain (Hains et al., 2010), cognitive deficits (Barrientos et al., 2010), addiction (Kelley and Dantzer, 2011), and mood disorders (Blank and Prinz, 2012). Finally, stressor evoked changes in microglia activation as a juvenile could increase one's vulnerability to experience negative consequences to later stressors (Bilbo and Schwarz, 2009).

In addition to stressor effects on myeloid cellular function, it is also clear that exposure to some acute or repeated/chronic psychological and/or physical stressors increase gene expression (Maslanik et al., 2012a) and concentrations of inflammatory proteins (Johnson et al., 2005b; Maslanik et al., 2012a; O'Connor et al., 2003; Persoons et al., 1995; Pertsov et al., 2009; Zhou et al., 1993) and complement proteins (Coe et al., 1988; Deak et al., 1997) in the blood and tissues. The role of inflammatory proteins and potential tissue inflammation in a plethora of disease states has fueled recent scientific interest into the effects that stressors have on these processes. Fig. 1C depicts the results of a PubMed search of the literature using the key words inflammatory proteins and stress. Clearly, the upturn in publication rate of papers investigating the impact of stressor on inflammatory proteins mirrors the sharp increase in publication rate focusing on stress and microglia (Fig. 1B). Taken together one can conclude that investigation of stress and 'aroused' innate immune processes has increased dramatically since 1990.

The impact of inflammation on disease in some tissues is clear. For example, cardiovascular disease is now considered to be an inflammatory disease (Kaplan and Frishman, 2001) and the changes in arterial and vascular structure and function are driven