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Invited minireview: Stress-induced remodeling of lymphoid innervation

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Abstract

Lymphoid organs have long been known to harbor neural fibers from the sympathetic division of the autonomic nervous system, but recent studies suggest a surprising degree of plasticity in the density of innervation. This review summarizes data showing that behavioral stress can increase the density of catecholaminergic neural fibers within lymphoid organs of adult primates. Stress-induced neural densification is associated with increased expression of neurotrophic factors, and functional consequences include alterations in lymph node cytokine expression and increased replication of a lymphotropic virus. The finding that behavioral stress can tonically alter lymph node neural structure suggests that behavioral factors could exert long-term regulatory influences on the initiation, maintenance, and resolution of immune responses.

Introduction

Behavioral processes regulate immune system function in part via direct sympathetic innervation of the spleen, lymph nodes, and all other primary and secondary lymphoid organs (Madden, Sanders et al. 1995; Bellinger, Lorton et al. 2001). Research on lymphoid innervation has generally presumed that acute changes in neural activity constitute the primary mechanism by which behavioral factors modulate release of the sympathetic neurotransmitter, norepinephrine (NE), from catecholaminergic varicosities within lymphoid tissue (Shimizu, Hori et al. 1994). However, a small number of studies have also documented structural alterations in the pattern of lymphoid innervation. Initial studies showed a progressive denervation of lymphoid tissue with aging and chronic inflammation (Bellinger, Madden et al. 2001; Kelley, Moynihan et al. 2003; Sloan, Tarara et al. 2006). Such results were not surprising, given the known inhibitory effects of inflammatory mediators on neuronal survival (Barker, Middleton et al. 2001; Kim, Beck et al. 2002; Ng, He et al. 2003), and age-related declines in expression of neurotrophic factors that sustain sympathetic nerve fibers (e.g., nerve growth factor; NGF) (Antonelli, Bracci-Laudiero et al. 2003). What has been more surprising is the

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recent discovery that lymph node innervation increases significantly in non-human primates subject to chronic social stress (Sloan, Tarara et al. 2006; Sloan, Capitanio et al. 2007b). This review surveys data on the molecular mechanisms that mediate stress-induced remodeling of lymphoid innervation, and considers the potential impact of these dynamics on basic biology of the immune system and the activity of lymphotropic pathogens. The perspective that ultimately emerges suggests that stress-induced remodeling of lymphoid innervation may function as a broad physiologic gain parameter that, 1.) imposes a long-term bias on immune responses, and 2.) sensitizes immunobiology to social and ecological conditions.

Lymphoid innervation

Post-ganglionic fibers from the sympathetic nervous system (SNS) enter lymphoid organs in association with the vasculature, and subsequently radiate into parenchymal tissues containing T lymphocytes and antigen presenting cells (APCs) (Bellinger, Lorton et al. 2001). In lymph nodes, these noradrenergic fibers course throughout the cortex, paracortex, and medulla, but they typically avoid B cell-rich follicles. Structural varicosities situated periodically over the length of these catecholaminergic fibers release micromolar concentrations of NE in response to stress and other stimuli (Shimizu, Hori et al. 1994; Madden, Sanders et al. 1995; Bellinger, Lorton et al. 2001). NE signals leukocytes via cellular β -adrenergic receptors, which activate the cAMP/PKA signaling cascade to alter antigen presentation, cellular activation, cytokine production, cell trafficking, and effector activities such as cellular cytotoxicity and antibody production (Kammer 1988; Ottaway and Husband 1994; Madden, Sanders et al. 1995; Carlson, Fox et al. 1997; Panina-Bordignon, Mazzeo et al. 1997; Sanders and Straub 2002; Saint-Mezard, Chavagnac et al. 2003). Effects on cytokine response are especially pronounced, with many studies suggesting that sympathetic activation can inhibit the expression of proinflammatory cytokines (Sanders and Kavelaars 2007), suppresses Th1 cytokines in favor of a Th2 profile (Panina-Bordignon, Mazzeo et al. 1997; Cole, Korin et al. 1998; Kohm and Sanders 1999; Maestroni and Mazzola 2003; Sanders and Kavelaars 2007), and inhibit the expression of Type I interferons (Collado-Hidalgo, Sung et al. 2006). The functional significance of these interactions is underscored by the fact that pharmacologic blockade of SNS activity can alter *in vivo* immune responses to model antigens and pathogen challenges (Madden, Moynihan et al. 1994; Kohm and Sanders 1999). The effects of physiologic variation in SNS activity are less well understood, but direct sympathetic innervation of lymphoid tissue is believed to represent a primary pathway by which behavioral processes can affect immune function *in vivo*.

Stress-induced remodeling

In the course of our studies on stress regulation of HIV-1 pathogenesis (Cole, Kemeny et al. 1996; Cole, Kemeny et al. 1997; Cole, Korin et al. 1998; Cole, Jamieson et al. 1999; Cole, Naliboff et al. 2001; Cole, Kemeny et al. 2003; Collado-Hidalgo, Sung et al. 2006), we recently examined the sympathetic innervation of lymphoid tissues in adult male rhesus macaques that were experimentally infected with the Simian Immunodeficiency Virus (SIV) (Sloan, Tarara et al. 2006; Sloan, Tarara et al. 2006; Sloan, Capitanio et al. 2007a; Sloan, Capitanio et al. 2007b; Sloan, Cox et al. 2007). HIV-1 and SIV are closely related lymphotropic retroviruses that replicate primarily in activated CD4⁺ T lymphocytes and macrophages within secondary lymphoid organs. Given previous *in vitro* evidence that NE can accelerate HIV-1 replication by up-regulating viral co-receptors (Cole, Jamieson et al. 1999; Cole, Naliboff et al. 2001), inducing viral gene transcription (Cole, Korin et al. 1998; Cole, Naliboff et al. 2001), and inhibiting antiviral cytokine responses (Cole, Korin et al. 1998; Collado-Hidalgo, Sung et al. 2006), we sought to determine whether SNS neural fibers might be plausible influences on viral replication within lymphoid tissue. We biopsied axillary and inguinal lymph nodes from adult male rhesus macaques after 39 weeks of daily social stress (unstable social conditions: 100 minutes of caging with 1-3 different conspecifics each weekday) or an equivalent amount

of non-stressful social interaction (stable social conditions: 100 minutes of caging with the same 2 conspecifics each day) (as detailed in (Capitanio, Mendoza et al. 1998; Sloan, Capitanio et al. 2007b)). Molecular histology supported the hypothesis that SNS activity enhances viral replication by showing a substantial increase in the transcription of SIV RNA in cells within 250 μ m of a catecholaminergic varicosity (Sloan, Tarara et al. 2006).

Comparison of lymph nodes from animals socialized under stable vs. unstable conditions also revealed a ~50% increase in the density of active SIV gene expression in socially stressed animals (Sloan, Tarara et al. 2006; Sloan, Capitanio et al. 2007b). We considered the hypothesis that increased catecholamine release from a fixed number of varicosities might enhance the local density of SIV gene expression, but found no significant elevation in SIV RNA density within 250 μ m of a catecholaminergic varicosity. Instead, we found an unanticipated ~50% increase in the lymph node-wide density of catecholaminergic varicosities in animals subject to chronic social stress. Quantitative analysis showed that the increased density of SIV replication in lymph nodes from stressed animals could be attributed almost entirely to the increased density of catecholaminergic varicosities within the lymph node parenchyma.

Analyses of lymph nodes from uninfected macaques yielded similar results, with tissues harvested from animals in unstable social conditions showing more than twice the density of catecholaminergic innervation observed under stable social conditions. Because these tissues were not subject to the inflammatory pathology of SIV infection, they provided a good context in which to estimate the general effect of social stress on lymphoid innervation. In tissues from animals socialized under either condition, fine-grain histological analyses showed the highest density of catecholaminergic innervation to be in the T cell-rich paracortex. This region also showed the most pronounced stress-induced increase in the density of catecholaminergic innervation. Medullary and cortical regions showed much sparser sympathetic innervation, and the density of that innervation was not significantly affected by social instability. The density of peri-vascular innervation was also unaffected by social conditions. Stress-induced hyper-innervation of the lymph node paracortex did not stem from any change in lymph node size or structural composition. Social conditions had no detectable effect on the total size of the lymph node, its cellular density, the relative distribution of T lymphocytes, B lymphocytes, macrophages, and follicular dendritic cells, or the relative size of the cortex, paracortex and medulla. Thus, these results indicated a surprising degree of socially-regulated neuroplasticity in the structural neurobiology of lymph nodes in adult primates, with a focal impact on one functionally specific region of the organ.

Molecular mechanisms

The density of peripheral sympathetic innervation is governed in large part by target organ expression of neurotrophic factors such as nerve growth factor (*NGF*) and brain-derived neurotrophic factor (*BDNF*) (Carlson, Albers et al. 1995; Kuruville, Zweifel et al. 2004; Bronzetti, Artico et al. 2006). Consistent with the hypothesis that stress increases lymphoid tissue innervation via increased neurotrophic support, we found increased expression of both *NGF* and *BDNF* in lymph nodes from animals socialized under unstable conditions. Statistical mediation analyses suggested that variations in *NGF* expression alone could account for more than 80% of stress-induced up-regulation of lymph node innervation. Quantitative analyses suggested that variations in *BDNF* did not play a substantial role in stress-induced hyper-innervation.

Sympathetic innervation can also be modulated by neuro-inhibitory factors such as interferon-gamma (*IFNG*), leukemia inhibitory factor (*LIF*), and Semaphorin 3c (Shirvan, Shina et al. 2000; Kim, Beck et al. 2002; Ng, He et al. 2003). However, none of those factors showed a stress-induced decrease that might permissively favor lymph node hyper-innervation. In fact, *IFNG* and *LIF* were substantially up-regulated in lymph nodes from stressed animals,

suggesting that the increased sympathetic innervation observed in those tissues occurred despite increasing expression of several neuro-inhibitory factors.

Together, these results suggest that *NGF* up-regulation plays a key role in driving the effects of social conditions on lymph node innervation (Carlson, Albers et al. 1995). Efforts to identify the signaling pathways that mediate these effects have been hampered by difficulties in identifying the cellular source of *NGF* within the lymph node. Analysis of isolated leukocytes indicate that both quiescent and activated mononuclear cells transcribe *NGF*, but this occurs at levels less than 1/10th the per-cell intensity observed in unfractionated lymph node tissues. These results imply that the stromal cells which provide a scaffold for trafficking leukocytes or perhaps the sympathetic fibers themselves might be primary *NGF* sources within the lymph node microenvironment. The later possibility is consistent with previous research indicating activity-dependent release of *NGF* from neurons (Zafra, Hengerer et al. 1990; Hasan, Pedchenko et al. 2003), and provides a plausible signaling pathway for transmission of social influences from the central nervous system into the peripheral lymphoid organs.

Functional impact

The physiologic role of lymphoid tissue innervation remains unclear, but the SIV infection model provides a rich context in which to consider this issue due to its well-defined immunopathogenesis. As reviewed above, unstable social conditions led to a significant increase in the lymph node-wide density of SIV replication that occurred specifically in the vicinity of parenchymal catecholaminergic varicosities. Replication of HIV-1 and SIV is controlled by both innate antiviral responses (e.g., Type I interferons, *IFNA* and *IFNB*) and adaptive cellular immune responses (e.g., viral-specific cytotoxic T lymphocytes). Analyses of Type I interferons showed a profound suppression in *IFNB* response to infection in lymph nodes from socially stressed animals (> 80% reduction) accompanied by a 4-fold increase in expression of *IFNA* mRNA (Sloan, Tarara et al. 2006; Sloan, Capitanio et al. 2007b). To assess the net impact of these two dynamics, we assayed the expression of interferon response genes that mediate *IFN* induction of the cellular “antiviral state” (e.g., *IFI27*) and found a substantial net suppression (> 50%). SNS suppression of innate antiviral response is consistent with previous *in vitro* analyses of beta-adrenergic regulation of *IFN* transcription (Collado-Hidalgo, Sung et al. 2006) and *in vivo* analyses of stress effects on systemic Type I interferon activity (Jensen and Rasmussen 1963; Chang and Rasmussen 1965). Moreover, quantitative mediational analyses of the SIV-infected lymph node data suggest that SNS inhibition of Type I interferon response could potentially account for more than 90% of the total relationship between sympathetic innervation density and SIV replication density. In the context of stress-induced up-regulation of lymph node sympathetic innervation, localized catecholamine suppression of Type I interferons provides an empirically verified mechanism for transmitting the effects of socio-environmental stressors into the molecular context of viral pathogenesis within the lymph node (Figure 1a). Presumably as a consequence of this SNS-mediated support for SIV replication within the lymphoid microenvironment, macaques socialized under unstable social conditions showed substantially lower circulating CD4⁺ T lymphocyte levels than those experiencing stable social conditions by 36 week post-infection (Figure 1b). Thus, lymphoid tissue neural dynamics appear to play a central role in the global effects of stress on the immunopathogenesis of SIV infection.

Open questions

Characterization of molecular causes and consequences of stress-induced lymphoid innervation is well underway in the context of lymphotropic SIV infection, but we still have more questions than answers regarding the more general physiologic significance of these dynamics for the broader function of lymphoid tissues as a structural catalyst for the initiation, maintenance, and resolution of adaptive immune response. Some prominent issues include:

How broad are these effects?—Is stress-induced densification of lymphoid innervation a general characteristic of most stressors? Or does it primarily occur with stressors that activate the SNS? Stimuli as diverse as loud noise and social reorganization have been found to up-regulate the density of neural fibers in solid tissues (Peters, Kuhlmei et al. 2005; Sloan, Tarara et al. 2006; Sloan, Capitanio et al. 2007b), but it is unclear what psychological or biological conditions are required for such effects. If stress-induced densification of sympathetic innervation is mediated by increased SNS activity, can non-stress sources of sympathetic activity (e.g., physical exertion) induce similar effects? How general are these effects across species? Stress-induced neural densification has already been documented for mice and macaques, suggesting a broad scope of impact within mammals. How broad are these effects across lymphoid organs? Do they occur in other lymph nodes besides the axillary and inguinal nodes already studied? Do they occur in spleen or gut-associated lymphoid tissues, or in primary lymphoid organs such as bone marrow or thymus? Sensory neural fibers within skin have already been found to arborize with stress (Peters, Kuhlmei et al. 2005), raising the possibility that peptidergic innervation of lymphoid organs might increase in parallel (Bellinger, Lorton et al. 2001).

What are the kinetics of stress-induced innervation?—Present results suggest that 10 months of social stress can substantially enhance sympathetic innervation of macaque lymph nodes. Analyses of peptidergic neural fibers in the skin suggest that some stressors might remodel tissue innervation in as little as 48 hrs (Peters, Kuhlmei et al. 2005). Determining the chronicity of stress required to remodel lymphoid innervation will provide a clearer picture of the breadth of circumstances in which these dynamics might apply.

How durable are these changes?—It is conceivable that transient stressors could induce long-term, persistent changes in lymphoid neural structure which permanently alter immune responsiveness. Alternatively, stress-induced densification might potentially equilibrate back to baseline levels once chronic stress resolves. “Pulse-chase” analyses testing the persistence of sympathetic hyper-innervation in the aftermath of stress will provide important information about the long-term impact on structural neurobiology of lymphoid organs. A related question involves the potential contribution of neurobiological critical periods. Are young individuals especially vulnerable to stress-induced hyper-innervation (as would be predicted from critical period neurobiology, and their more robust basal innervation) or are older individuals potentially more vulnerable due to their lower neurotrophin expression and a background of age-related denervation? Neurobiology aside, how durable are impacts of these changes on the nature of immune responses? For example, are cytokine polarizations induced during a period of dense innervation “locked in” over the lifespan of the lymphocytes activated during that period? Or, does the immune system rapidly re-model its regulatory interactions following resolution of stress-induced hyper-innervation?

Which neurotrophins are responsible?—Current results suggest a strong relationship between *NGF* up-regulation and stress-induced arborization of sympathetic innervation in lymphoid tissue (Carlson, Albers et al. 1995; Sloan, Tarara et al. 2006; Sloan, Capitanio et al. 2007b; Sloan, Nguyen et al. 2007). However, it is conceivable that other neurotrophic factors known to regulate sympathetic innervation might also participate (e.g., NT3 or BDNF, both of which have been detected in our studies of lymph node gene expression) (Sloan, Tarara et al. 2006; Sloan, Capitanio et al. 2007b; Sloan, Nguyen et al. 2007). Demonstration of a causal role for *NGF* will require direct molecular manipulations (e.g., via anti-*NGF* neutralizing antibodies or analysis of receptor knock-out animals).

How are neurotrophins being regulated?—Which cells are responsible for stress-induced up-regulation of *NGF*, and what signals drive that expression? As noted above,

analysis of macaque peripheral blood mononuclear cells suggest that lymphocytes are not the primary contributor (< 10% of total lymph node *NGF* transcription), and catecholamines do not substantially up-regulate *NGF* expression by leukocytes (Sloan, Capitanio et al. 2007b; Sloan, Capitanio et al. 2007a; Sloan, Cox et al. 2007; Sloan, Nguyen et al. 2007). Perhaps sympathetic varicosities are themselves the major *NGF* releasers in the lymph node (Zafra, Hengerer et al. 1990; Hasan, Pedchenko et al. 2003)? If so, activity dependent-release of *NGF* from sympathetic fibers would provide a plausible transmission pathway from the central nervous system, as well as an autocrine stimulus for sympathetic arborization (Hasan, Pedchenko et al. 2003). Some evidence suggests that activated APCs might also express *NGF* at high levels (Garaci, Caroleo et al. 1999), and this could explain why sympathetic innervation (and its stress-induced up-regulation) is most pronounced in the paracortex (the primary site of antigen presentation to T cells). Under this hypothesis, however, the mechanism by which information about social conditions makes its way into lymphoid tissue requires further definition. Perhaps a positive feedback cycle develops in which sympathetic neural activity increases the activity of APCs, which subsequently release *NGF*, which acts to selectively maintain paracortical sympathetic fibers (Heumann 1987).

What other factors influence innervation?—The present studies show that stress can enhance lymph node innervation independently of any detectable pathology (e.g., in animals not subject to any experimental infection). However, lymphotropic viral infections can denervate lymphoid tissues (Kelley, Moynihan et al. 2003), and similar effects have been observed in the context of SIV infection (Sloan, Nguyen et al. 2007). These dynamics raise the possibility that localized inflammatory signaling might contribute to the dynamic equilibrium of sympathetic innervation. Given evidence that beta-adrenergic signaling can inhibit several pro-inflammatory cytokines (particularly Type I and II interferons) (Panina-Bordignon, Mazzeo et al. 1997; Cole, Korin et al. 1998; Collado-Hidalgo, Sung et al. 2006), it is conceivable that sympathetic activity might indirectly promote lymphoid innervation by suppressing the neural-inhibitory activity of interferons (Kim, Beck et al. 2002). Simultaneous assessment of neurotrophin and cytokine signaling are needed to comprehensively define physiologic determinants of sympathetic innervation. Parallel assessment of lymphoid organ volume, structure, and cellularity are critical to discriminate true changes in neural arborization from relative alterations in innervation density that might stem from acute changes in organ volume relative to a fixed complement of neural fibers.

What is the impact on immune function?—Analyses indicate substantial inhibition of Type I interferon response (Sloan, Capitanio et al. 2007a; Sloan, Capitanio et al. 2007b), but scores of other cytokines and cellular processes might also be regulated by localized alterations in sympathetic innervation. Given lymphoid organs' fundamental physiologic role as sites for antigen presentation, activation of B and T lymphocytes, and the polarization of cytokine responses, it seems unlikely that the immunobiological effects of stress-induced hyper-innervation will be limited to the suppression of the innate antiviral response.

The focal effects of stress on the density of sympathetic varicosities within the paracortex suggests that a major immunoregulatory target involves interactions between T lymphocytes and APCs (Willard-Mack 2006). Behavioral stress is known to amplify the antigen presenting activity of dendritic cells (Saint-Mezard, Chavagnac et al. 2003), and to alter their production of cytokines that ultimately polarize T cell cytokine responses (Maestroni and Mazzola 2003; Saint-Mezard, Chavagnac et al. 2003). To the extent that stress enhances sympathetic innervation of the paracortex, this may impose a long-term bias on the nature of adaptive immune responses that emerge from that microenvironment during periods of chronic stress (e.g., Th1/Th2 polarization, the induction of cytotoxic T lymphocyte vs. B lymphocyte / antibody responses, the resolution of acute immune responses, and the establishment of long-term memory) (Sanders and Kavelaars 2007). Genetic manipulation of lymph node innervation

has also been found to affect lymphocyte recruitment and retention (Carlson, Fox et al. 1997), suggesting another kinetic parameter of T cell / APC interaction that might be altered in response to SNS activity. It is intriguing that basal sympathetic innervation and stress-induced hyperinnervation selectively avoid B cell regions of the lymph node cortex (follicles) and medulla. This suggests that functional interactions between APCs and T lymphocytes might represent the key physiologic target of lymph node sympathetic innervation.

How can we protect against detrimental effects of stress-induced innervation?

—Beta-blockers can abrogate many effects of SNS activity on leukocyte biology, and preliminary studies suggest these drugs penetrate into the lymph node parenchyma (Sloan, Cox et al. 2007). However, paradoxical responses have been observed, including up-regulation of leukocyte beta-adrenoreceptors and enhanced density of catecholaminergic varicosities (neither entirely unexpected based on previous effects of beta-blockers on other tissues). Given that sympathetic fibers can also release neuropeptides that are not antagonized by beta-blockers (e.g., neuropeptide Y) (Bellinger, Lorton et al. 2001), these compensatory neural reactions to beta-adrenergic blockade might have unintended impacts on lymph node biology. If beta-blockade is not an effective strategy for abrogating the adverse impacts of stress-induced lymphoid hyper-innervation, what other pharmacologic or behavioral interventions might prove more effective?

What is the teleologic significance of dynamic lymphoid innervation?—The physiologic rationale for stress-dependent remodeling of sympathetic innervation will be greatly clarified by, a.) the identification of its leukocyte functional target(s), and, b.) discovery of the signaling pathways that transmit the experience of stress into peripheral lymphoid tissues. Nevertheless, some speculations are possible based on the evidence already available.

Based on the functional and anatomical considerations outlined above, it seems likely that APC regulation of T lymphocyte responses is a primary immunologic target. Given the relatively slow kinetics of neural sprouting (hours to days), and the general hypothesis that NGF acts by maintaining randomly evolved neural structures (rather than actively recruiting those structures) (Heumann 1987), any immunobiological “bias” that results from stress-induced innervation is likely to emerge slowly and be relatively persistent (e.g., maintained over the course of days, rather than hours or minutes). A speculative extrapolation of these observations suggests that stress-induced remodeling of lymphoid sympathetic innervation might exist primarily to impose a long-term regulatory “bias” on the nature of T cell-mediated adaptive immune responses that emerge during periods of persistent organismic threat. The exact nature of that bias remains to be defined by direct manipulations of sympathetic innervation, but the existing literature suggests that enhanced antigen presentation with a Th2 / humoral skew might be one teleologic objective (Sanders and Kavelaars 2007). Given that similar dynamics might be induced by acute SNS activation (i.e., short-term changes in NE release from existing varicosities), long-term remodeling of SNS innervation may occur primarily to extend the temporal scope of such influences.

An alternative (and not exclusive) hypothesis involves the possibility that lymphoid tissue remodeling of sympathetic innervation might function as a broad neurobiological “gain parameter” to increase the throughput of information from the central nervous system into the peripheral biology of lymphoid organs. By increasing the arborization of sympathetic neural projections in lymphoid organs, stress-induced remodeling would functionally increase the number of catecholamine point sources that respond to activation of single neural soma. This would essentially increase the “volume” of sympathetic signaling to lymphoid tissue, and potentially magnify its functional impact. From this perspective, stress-induced hyper-innervation may serve to sensitize the immune system to inputs from the sympathetic nervous system during periods of recurrent threat.

The discovery of stress-induced innervation dynamics in the context of persistent social stress raises the possibility that these neurobiological dynamics might have evolved specifically to modify host resistance to socially-mediated health challenges. Ethological perspectives emphasize the role of social factors and lifestyle strategies in optimizing individual selective fitness. From this perspective, close interactions with conspecifics represent a primary path for the spread of infectious disease, and it is conceivable that neural regulation of immune response might have evolved as a physiologic mechanism for optimizing host resistance to infection under changing social conditions (e.g., in the presence of socially mediated threat vs. support). Previous research has suggested that the *quantity* of social interactions can influence health outcomes (Seeman 1996; Cohen, Doyle et al. 1997). In holding the quantity of social interaction constant, the recent macaque studies have shown that the specific *nature* of social interactions plays a critical role in governing neurobiological and immune adaptation (Sloan, Tarara et al. 2006; Sloan, Capitanio et al. 2007b). In the context of an evolutionary history shaped by socially-transmitted infectious disease, social regulation of immune response could provide a mechanism for “hedging one's bets” in optimizing the immune response under different exposure regimes.

Regardless of the teleologic basis for stress-induced remodeling of lymphoid innervation, recent results reveal a surprising degree of behaviorally-induced plasticity in the structure of lymphoid innervation. These findings define a novel pathway by which social factors can modulate immune response and viral pathogenesis, and they motivate new inquiries into the determinants and consequences of lymphoid tissue innervation by the sympathetic nervous system.

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Figure 1.

a.) Hypothesized model of social stress effects on *NGF* expression and catecholaminergic innervation of primate lymph nodes, resulting in suppressed Type I interferon response to infection, enhanced SIV replication, and accelerated progression to clinical immunodeficiency.

b.) Impact of stable vs. unstable social conditions on circulating CD4+ T lymphocyte levels 36 weeks after SIV infection.