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Tumor necrosis factor receptor 1 and 2 (TNFR1/R2) deletion provoke inflammatory chemokines, cytokines and pain related hypersensitivity

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Chronic inflammation of mucosal surface is an aberrant immune response to different chemical, environmental insults as well as luminal microbial which generate an array of cytokine and chemokines and oxygen radicals leading to tissue destruction and loss of function, as noted in pancreatitis, hepatitis, inflammatory bowel diseases (IBD), periodontitis, arthritis and temporomandibular joint disorders (TMJD). Patients with TMJD and arthritis often have a combined etiology of hereditary and microenvironmental factors contributing to joint pain. Multiple clinical and animal studies have proven "dual-hit phenomenon" as inflammatory insults to initiate chronic response in joints and in other related as well as unrelated organs. As, the initial inflammatory insult primes the immune system, the succeeding insult/s amplify/s deleterious responses. Pro-inflammatory cytokine, tumor necrosis factor α (TNFα) up-regulates various inflammatory markers, cytokines and chemokines to initiate acute and chronic stages of inflammation and pain related sensation in patients and model for pancreatitis, hepatitis and IBD, as well as neuropathy. TNFα is released mainly by activated macrophages, astroglia, microglia, CD4+ lymphocytes, natural killer cells, and neurons. The biological action of TNFα is through two gene family receptors, TNFR1 and TNFR2. Dysregulation of TNFα contributes to development of colitis, hepatitis, pancreatitis, headache, periodontal, temporomandibular and neuropathic pain. Trigeminal neuropathic pain is common following trigeminal nerve damage post-surgical procedures and maxillofacial injuries. Soluble TNFR1 and R2 neutralize circulating TNFα to alleviate pain related responses such as allodynia, hyperalgesia or peripheral nerve injuries. Murine with genetic deletion of TNFα receptors (TNFR1/R2 deficient) develop severe chronic inflammatory symptoms including pancreatitis and orofacial trigeminal inflammatory compression (TIC) nerve injuries compared in WT animals. In addition, TNFR1/R2 deficient animals after recovering from initial inflammatory insult, such as knee joint arthritis or unilateral into temporomandibular joint (TMJ), when exposed to second but unrelated, colonic inflammatory, insult, develop recrudescence chronic secondary hypersensitivity which continued for over 4-6 months duration of studies. Analysis of proteomic profiling at multiple time points identified several altered levels of inflammatory cytokines and chimokines. This presentation will discuss in detail relationship between TNFα and its receptors to provoke chronic inflammatory and neuropathic disorders and further to expose their association with several other inflammatory markers through proteomic profiling. In addition, various pharmacological interventions will be scrutinized for efficacy in these chronic hypersensitive models.

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