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Editorial: Cytokines in inflammation, aging, cancer and obesity

This special issue contains a collection of articles that describe various cytokine-associated pathologies and mechanisms involved. As the key messengers of information relay in the body, cytokines play crucial roles in development, homeostasis and physiological functions. Under pathological conditions, changes in cytokine production and bioavailability orchestrate the body's defense against invading pathogens or altered functions in an effort to re-establish homeostasis. Sometimes these cytokine networks go awry, contributing to diverse pathologies. The CIACCO symposium began as a small gathering of Québec (Canada) researchers working on diverse disease models to create a forum to discuss cytokines, cytokine signaling and its dysregulation, with the goal of benefitting from each other's expertise and promoting knowledge integration and synthesis of new ideas. The acronym CIACCO stands for Cytokines in Inflammation, Aging, CanCer and Obesity, reflecting the interests of the research groups involved in this initiative. This diversity is reflected in the articles assembled in this special issue.

Allergies and asthma continue rising in the western world [1]. These acute inflammatory reactions are induced by allergens and are mediated by type-2 immune response (so-called because of the differentiation of activated $CD4^+$ T cells toward Th2 type cells) [2]. However, asthma and asthma exacerbations are also induced by respiratory viral infections [3]. In the majority of virus-induced type-2 immune response, the underlying mechanisms remain unexplained. Recent advances point to the active role of innate lymphoid cells (ILCs) in all types of adaptive immune responses [4]. ILCs are distinct groups of lymphocytes that lack lineage specific T cell markers and T cell antigen receptor yet display cytokine profiles resembling those of classical Th1, Th2 and Th17 cells. Based on the transcription factors underlying their differentiation and cytokine profile, ILCs are classified into ILC1 (IFNγ), ILC2 (IL-5, IL-13) and ILC3 (IL-17, IL-22) groups [5,6]. It has become clear that ILC2 cells are the key mediators of type 2 immunopathology associated with allergic inflammatory responses such as asthma, atopic dermatitis and respiratory distress induced by viral infections. Fritz and colleagues review the various positive and negative regulators of ILC2 in type 2 immunopathologies at the mucosal surfaces, and the critical role of interferons in this regulation [7].

Chronic viral infections such as human immunodeficiency virus (HIV) and hepatitis virus are characterized by impaired activation and differentiation, or exhaustion of $CD8^+$ T lymphocytes [8–10]. Cytokines play crucial roles in shaping $CD8^+$ T cell responses [11,12]. In this issue, two reviews highlight recent progress toward understanding cytokine-mediated modulation of T cell functions. Beltra and Decaluwe describe how certain cytokines contribute to the development of T cell exhaustion, which may have evolved as a mechanism to thwart tissue damage caused by persistent T cell activation during chronic viral infections, and how other cytokines could be exploited to reverse this state and reinstate functional anti-viral T cell responses [13]. Richer and colleagues provide an update on cytokine-dependent modulation of effector $CD8^+$ T cell functions, particularly the role of inflammatory cytokines. They also propose that certain inflammatory cytokines, for example, IL-15 induced by type-I interferons, may function as an early warning system to alert the memory T cell pool, and in doing so, facilitate robust expansion of antigen specific T cells [14].

Reconstitution of T cells has important clinical applications in immunodeficiency states caused by infections (HIV), treatment of malignancies or following organ transplantation [15]. Cytokines have a central role in all approaches aimed at restoring T cell numbers. Particularly, IL-7 and IL-15, which are essential for T cell development in the thymus and for maintaining naïve and memory T cell compartments in the periphery, are being evaluated clinically for restoring a functional immune system in immunocompromised individuals [16,17]. Guimond and colleagues discuss the negative aspects of using IL-7 and IL-15 to improve immune reconstitution after allogeneic stem cell transplantation, wherein these cytokines also promote graft versus host disease [18]. They also highlight the potential utility of the chemokine CXCL-12 (SDF-1α) in alleviating these side effects. Diminishing immune functions and increased susceptibility to infections are also the consequences of physiological aging, resulting from thymic involution, reduced repertoire diversity of the peripheral T cell pool and impaired B lymphocyte functions [19,20]. Various approaches such as treatment with IL-7 and keratinocyte growth factor are being tested clinically to rejuvenate the declining thymic functions. Rafei and colleagues discuss the role of another γ_c-utilizing cytokine, IL-21, in boosting thymopoiesis. IL-21 has been very well studied in the context of its essential role in antibody production and preventing $CD8^+$ T cell exhaustion, and in autoimmunity [21,22]. The findings of Rafei and colleagues indicate that IL-21 treatment of aged mice boosts thymocyte progenitor cells and T cell maturation and emigration to the periphery, raising the possibility of using IL-21 to restore T cell functions upon aging and following iatrogenic damage to the thymus [23].

Regulation of cytokine signaling is critical to control the potential of many cytokines to cause a wide-range of pathologies including autoimmunity and cancer [24]. This regulation is achieved at many levels namely, downregulation of receptor chains, release of soluble receptors and decoys, recruitment of phosphatases to the activated receptor chains to inactivate the JAK kinases, induction of feedback inhibitors such as SOCS proteins that attenuate signal transduction, blockade of nuclear translocation of STAT transcription factors or inhibition of their activities by the PIAS molecules [24,25]. Ali Ahmad and colleagues describe the importance of the IL-18 binding protein (IL-18BP), a natural regulator of IL-

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18 bioactivity, in preventing tissue destruction, and elaborate how impaired production of IL-18BP contributes to the pathogenesis of HIV infection [26]. Pike and Tremblay discuss the role of protein tyrosine phosphatases (PTP) in regulating cytokine signaling with particular emphasis on PTPN1 (PTP1B) and PTPN2 (TC-PTP) in lymphoid malignancies [27].

Members of the SOCS family proteins are important feedback inhibitors of the JAK-STAT signaling pathway [28]. SOCS1 and SOCS3 are implicated regulating the innate and adaptive arms of the immune system by preventing aberrant activation of macrophages and T lymphocytes [29]. These two SOCS proteins are also implicated in regulating growth factor signaling *via* receptor tyrosine kinases [30]. The diversity of SOCS-regulated signaling pathways implicates them in maintaining homeostasis at cellular, organ and organismal levels. In this issue, Kandhi et al., show that SOCS1 is an important regulator of liver fibrosis and describe a role for SOCS1 in regulating growth factor signal transduction in hepatic stellate cells [31].

Many tumors repress the SOCS1 gene by epigenetic mechanisms such as promoter CpG methylation and by miRs such as miR-155, miR-19 and miR-30d. Hence, SOCS1 is considered a tumor suppressor in lymphoid cells and several non-lymphoid cell types [32]. The tumor suppressor mechanisms of SOCS1 operate via regulation the JAK-STAT and RTK signaling pathway as well as via other mechanisms such as co-operation with the tumor suppressor p53 and regulation of the oncogenic potential of the cell cycle inhibitor $p21^{CIP1}$ (CDKN1A) [33,34]. Mukhopadhyay et al., report that the STAT5 transcription factor, an upstream activator of SOCS1, is induced by the p53 tumor suppressor following DNA damage [35]. Since SOCS1 can activate p53 [33], the authors propose a positive feedback mechanism that may halt cancer progression resulting from aberrant cytokine stimulation [35]. Restoring SOCS1 expression is therefore considered as a promising cancer therapeutic approach. Miganacca and colleagues describe the development of miR-sponges to antagonize miR-155 and miR-19 in an effort to restore SOCS1 expression in tumor cells [36]. Even though SOCS1 is generally considered a tumor suppressor, there are instances where certain oncogenic pathways exploit SOCS1 to promote tumorigenesis, and SOCS1 overexpression does not lead to growth suppression [37,38]. Such a scenario has been documented for other well-known tumor suppressor molecules and pathways, for example, $p21^{CIP1}$ and the TGFβ pathway [39,40]. Saucier and colleagues document the evidence for the paradoxical oncogenic potential of SOCS1 in cancers [41].

This decade is witnessing the emergence of obesity and its complications namely, insulin resistance, type 2 diabetes, liver diseases, dyslipidemia, atherosclerosis and related cardiovascular diseases, as a major healthcare burden [42–44]. While healthy eating and an active lifestyle are the primary and the most effective ways to prevent obesity and reverse early stages of the deregulated metabolic state, patients with advanced disease will benefit from therapeutic intervention [45]. Inflammatory cytokines, which play a key role in perpetuating a vicious cycle of chronic inflammation in adipose tissues, are a potential therapeutic target in obese patients [46,47]. Besides, by targeting inflammation in obesity, these treatments could also thwart obesity-associated cancer development [48]. In this issue, Cepero-Donates and colleagues demonstrate the pathogenic role of IL-15 in promoting lipid accumulation in the liver following diet-induced obesity, and show that this is accompanied by IL-15-dependent increase in chemokine gene expression and infiltration of immune cells [49]. In an accompanying paper, the same group shows that IL-15 derived from macrophages and hepatocytes are critical for maintaining NK and NKT cell subsets in the liver, but the loss of hepatic IL-15 does not abrogate the systemic IL-15-dependent development of fatty liver disease [50].

While innate immune cells are the major source of the inflammatory cytokine production in obese adipose tissues, adaptive immune cells also contribute to perpetuating the inflammatory cascade. Thibodeau and colleagues provide an overview of the role of antigen presenting cells and the adaptive arm of the immune response in this pathogenic process [51]. Inflammatory cytokines such as IL-6 in general decrease glucose utilization and contribute to the development of insulin resistance and obesity [47]. On the other hand, cytokines such as ciliary neurotrophic factor, carditropin-1 and oncostatin M, which utilize the gp130 chain of the IL-6 receptor for signaling, exert anti-obesity roles by reducing food intake, inhibiting adipogenesis or increasing glucose uptake, as summarized by Pasquin et al., in a brief review [52].

Pleiotropism is a well-recognized attribute of many cytokines. However, it is not uncommon that a particular cytokine or growth factor is extensively studied in the context of specific functions in certain cell types and tissues than others. Often, the less well-known functions of these cytokines are drowned in the din of its primary focus, and fail to get the attention they deserve. One such example is hepatocyte growth factor, which has been extensively studied for its physiological functions in embryogenesis, organogenesis, tissue repair, oncogenesis and metastasis [53,54]. Several recent studies have renewed the interest in HGF-MET axis within the immune system. These include the potential role of HGF in promoting thymopoiesis, T cell reconstitution and immune tolerance [55–57]. The last article reviews in detail the functions of HGF-MET signaling in various cell types of the immune system [58].

The CIACCO-2015 symposium has largely succeeded in its goal to bring together a diverse array of cytokine research under one roof. The CIACCO acronym also signifies the need for such cross-disciplinary interaction in advancing cytokine biology: *Ciacco* is a character in the Divine Comedy by Dante Alighieri, but his identity and true nature were not clearly described. The way Ciacco presents himself to Dante in Hell allows various interpretation of his character – both good and bad. Likewise, cytokines can exert both good and deleterious effects, and these effects are interpreted in different ways depending on the context. By bringing these ideas together, the CIACCO-2015 symposium has succeeded in making a small but significant contribution to the advancement of cytokine biology.

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