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# Cytokine receptor signalling and aging

T. Fulop [a,b,*], A. Larbi [a], N. Douziech [a], I. Levesque [a], A. Varin [b], G. Herbein [b]

[a] Centre de Recherche sur le vieillissement, Service de Gériatrie, Département de Médecine, Université de Sherbrooke, Sherbrooke, Que., Canada
[b] Department of Virology, EA3186, IFR133, Franche-Comté School of Medicine, Besançon, France

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**Abstract**

With ageing the immune system is deregulated and this leads to the development of immunosenescence mainly affecting the adaptive immune response. There is much knowledge accumulated concerning various receptor functions and signalling with ageing such as TCR, FcRs, TLRs. Cytokines are playing a major role in haematopoietic cell functions and in the harmonious and integrated coordination of the innate and adaptive immune response. There exists a large amount of data on cytokine production changes with ageing, as IL-2 production is decreasing, while IL-6 production is increasing. In contrast, there is only scarce knowledge concerning the cytokine receptors and their signalling in ageing. However, there is some evidence that the signalling of IL-2 receptors is altered in T cells and macrophages, mainly in relation to the JAK/STAT pathway. We present here evidence that the IL-6 induced signalling is also altered in T cells with ageing. An alteration in the JAKs and STATs activations in T cells and macrophages was demonstrated. The exact cause of these altered activations is not known and future studies are needed to elucidate them. In this review we summarise our present knowledge on cytokine signalling with ageing, mainly focusing on IL-2 and IL-6 receptors signalling.


*Keywords:* T cells; Macrophages; Ageing; Immunosenescence; Cytokine receptors; JAK/STAT; IL-2; IL-6

## 1. Introduction

Cytokines are major mediators of the immune response. Cytokines control many different cellular functions including proliferation, differentiation, cell survival/apoptosis and numerous gene expression (Auernhammer and Melmed, 2000; Murphy et al., 2000). Moreover, they also participate in several pathophysiological processes such as viral infections, autoimmune diseases and InflammAging (Jiang et al., 2000; Aringer et al., 1999; Franceschi et al., 2000). They are synthesized under various stimuli by different cells of the innate immune response such as monocytes, macrophages, dendritic cells and of the adaptive immune response such as T and B lymphocytes. Cytokines may be classified as pro-inflammatory derived mainly from the innate immune cells and Th1 cells including IFNgamma, TNFalpha, IL-1, IL-6 or anti-inflammatory mainly synthesized by the Th2 immune cells including IL-10, IL-4, IL-13, IL-5. These different cytokines independently of their physiological actions will elicit their response on acting through specific receptors. However, a wide range of the cytokine receptors is common to a family of cytokines and the specificity is assured by the individual receptor subunit alpha. Different cytokine receptors utilize various combinations of JAKs and STATs to transduce their signals.

It is well known that with ageing a decrease in the immune response is occurring involving both part of the immune response, i.e. innate and adaptive (Grubeck-Loebenstein and Wick, 2002). Nevertheless, the actual paradigm states that the adaptive immune response is more altered and this will induce and determine the alterations encountered in the other parts of the immune system.

This review will describe alterations related to cytokines, especially of IL-2 and IL-6, and their signalling in T cells and macrophages with aging, with a succinct comparison with what is occurring in the brain.

## 2. Immunosenescence

Various changes occur in the immune system with advancing age, contributing to the dysfunction of the immune response (Grubeck-Loebenstein and Wick, 2002). This decrease in the immune response leads to the increased incidence of infections,

* Corresponding author at: Research Center on Aging, University of Sherbrooke, 1036, rue Belvedere Sud, Sherbrooke, Que., Canada J1H 4C4. Fax: +1 819 829 7141.
*E-mail address:* tamas.fulop@usherbrooke.ca (T. Fulop).

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autoimmune disorders, cancers and chronic inflammatory processes such as atherosclerosis, Alzheimer's disease (Castle, 2000; Wick et al., 2000; Fulop et al., 2005). The most important changes seem to occur in the adaptive immune system affecting mainly the T lymphocytes. It has been demonstrated that even with healthy aging important functions of T cells are altered. The most important are the production of IL-2 and the proliferation.

The decrease in the production of IL-2 leads to a decrease in the clonal expansion of T cells leading to a decrease in the specific immune response. This situation creates an unbalance between the adaptive and innate immune response. Some specific functions of the innate immune response have also been demonstrated to be altered with ageing (Fulop et al., 2004). Most importantly the innate immune response, probably to compensate the decreased production of Th1 cytokines and the increased Th2 cytokines production by the adaptive immune system, is producing a large quantity of Th1 type cytokines, including TNFalpha, IL-1, IL-6. This situation seems to lead to a pro-inflammatory status known as the Inflamm-Aging. This situation is even more accentuated in pathological aging circumstances such as frailty (Leng et al., 2004; Joseph et al., 2005), as well as in age-related diseases including Alzheimer's disease (Chong et al., 2005). Thus, there are profound changes in the cytokine milieu with aging (Castle et al., 1999; Caruso et al., 2004).

Although the thymic involution contributes to the altered immunoresponsiveness with aging, two other major features of immunosenescence are (i) changes in T cell phenotypes and (ii) reduced T cell activation response (Fulop et al., 2005). One of the most consistent alterations noted in T cells with aging is the decrease of the proportion of T cells with naïve phenotype with a concomitant increase in T cells with activated memory phenotype (Effros and Pawelec, 1997). The other most consistent finding is the T cell hyporesponsiveness to various stimulations with aging. The observed functional changes include decreased T cell proliferation and IL-2 production, shift in cytokine production from Th1 to Th2. These functional alterations of T cells are mainly due to changes in the signal transduction of the TCR and CD28 receptors (Pawelec et al., 2001).

T cells become activated as a result of recognition of antigenic determinants presented by professional APC to the TCR within restriction of the MHC. The activation of protein tyrosine kinases (PTK) and the mobilization of $Ca^{2+}$ are the earliest biochemical events that can be detected following the engagement of the TCR (Guse, 1998). $p56^{lck}$ (Lck), a member of the *src* family of PTK, is crucial to the initiation of signal transduction and targets immunoreceptor tyrosine-based activation motifs of the CD3 complex and the ζ-dimer. ZAP-70 is recruited to the ζ-dimer and phosphorylated by Lck (Walk et al., 1998). Activated ZAP-70 phosphorylates LAT which becomes a scaffold protein for the recruitment of multiple partners including the adaptor proteins Gads and Grb2 and the enzymes of phospholipid metabolism PI3K and PLCγ1 (Kane et al., 2000). Although the engagement of the TCR provides an essential signal to T cells (signal 1), commitment to proliferation and differentiation will not occur unless a secondary signal (signal 2) is provided by ligation of CD28 (Frauwirth and Thompson, 2002). A number of components of the T-cell activation complex are recruited to plasma membrane microdomains that are termed lipid rafts or Detergent Resistant Membranes (DRM). Current evidence suggests that DRM provide a platform for the recruitment of proteins involved in the formation of the initial steps of T-cell signaling (Alonso and Millan, 2001).

It is now well-established that aging is associated with a decline in T cell activation and consequently in proliferation with a decline in CD28, but not TCR expression. Moreover, several studies have shown defects in the early events of the T-cell signaling cascade with aging in mice and humans (Signal 1) (Miller et al., 1997; Pawelec et al., 2001). These defects include tyrosine phosphorylation of signaling proteins, calcium mobilization, activation of the MAPK and JNK pathways, translocation of NF-ATc to the nucleus, IL-2 production and T-cell proliferation. Our group and others have previously demonstrated alterations in signal transduction in T lymphocytes with human aging, mainly in CD4+ T cells. We demonstrated for the first time an alteration in SLP-76 activation in DRM with aging (Fülöp et al., 2002). Recently, we extended our study to other signaling molecules and focused on cholesterol in DRM. We found that the cholesterol content of lipid rafts was significantly higher in T-cells from elderly subjects as compared to young individuals. Confocal microscopy revealed a defect in the coalescence of lipid rafts in T-cells of aged subjects exposed to mAb directed against CD3 or a combination of CD3 and CD28 (Larbi et al., 2004a). In the mean time the signalling of CD28 is also dramatically changed in CD4+ T cells, affecting mainly Akt activation (Larbi et al., 2005, manuscript submitted). These alterations are related to changes in the cell membrane composition (Larbi et al., 2004a).

As there exists signalling alterations in many T cell receptors as well as other receptors in the central nervous system including dopamine and acetylcholine, the question arises whether the cytokine receptors could make an exception to this rule. We will mainly describe here the IL-2 and IL-6 receptors related signalling changes with aging.

## 3. Cytokines, cytokine receptors and ageing

Cytokines, such as IL-2 and IL-6 as well as many others mediate their signal after binding the respective membrane bound cytokine receptors through the activation of several cytoplasmic proteins.

These receptors, especially of IL-2, are composed of three distinct subunits: IL-2Rα (CD25), IL-2Rβ (CD122) and IL-2Rγ. The IL-2Rβ chain is expressed constitutively in NK cells and cytotoxic T cells, but not in helper T cells, but is inducible upon activation. The γ chain is expressed constitutively in monocytes and lymphoid cells. In contrast, IL-2Rα is normally never expressed in the absence of its haematopoietic receptor family partners in lymphoid cells (Eicher et al., 2002). The γc chain as a member of the cytokine receptor superfamily contains conserved regions as well as Box1 and Box2 domains.