NK Cells in Human Ageing

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Contents

Abstract: NK cells are cytotoxic lymphocytes that are involved in the early defense against virus infected and tumor cells. NK cells exhibit the capacity to distinguish normal and damaged cells as well as self- and foreign cells. Besides their cytotoxic capacity NK cells also regulate the immune response by producing cytokines and chemokines that directly participate in the elimination of pathogens or activate other cellular components of immunity. NK cells express a broad range of activating receptors and their function is controlled by inhibitory receptors specific for the MHC class I molecules that are ubiquitously expressed on target cells.

Several alterations have been described in human NK cell function with advancing ageing, therefore contributing to immunosenescence. Thus whereas healthy elderly, including centenarians, have preserved NK cell number and function, a decrease in NK cell activity is associated to increased incidence of infectious and inflammatory diseases and to increased risk of death due to infection. Here, we describe recent data about the effects of ageing on NK cells.

Keywords: Ageing • Immunosenescence • NK cells • Cytokines • NK cell ceptors

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1 Introduction

Although it had been generally accepted that some aspects of innate immunity, are well preserved in ageing (Pawelec et al. 1998), cumulative evidences in the last decade support the existence of age-associated changes in the cellular components of the innate immune system, including NK cells, that are important in the increased susceptibility of elderly individuals to infectious diseases (Delarosa et al. 2006; Solana et al. 2006).

2 Natural Killer Cells

Natural killer (NK) cells are bone marrow-derived lymphocytes that participate in the early defense against intracellular pathogens and tumor cells. NK cells are part of the innate immunity arsenal and have been defined as cytotoxic non-T lymphocytes. The most important characteristic that distinguishes T-cells from NK cells is the T-cell antigen receptor (TcR) which is made from rearranging genes and is clonally expressed (Parham 2006). NK cells act within hours of infection in contrast to T-cells that require several days to arise. NK cells are characterized by the expression of CD56, an isoform of the neural cell adhesion molecule (N-CAM) and/or CD16, the low-affinity IgG Fc receptor (FcγRIIIa). The discovery on NK cells of receptors for polymorphic major histocompatibility complex (MHC) class I molecules has contributed to better understanding of NK cell biology. In spite of this, NK and T-cells have much in common: cell-surface molecules, effector functions as cytokine secretion and cytotoxicity. Many of the cell surface molecules we called NK cell associated receptors (NKR) are also expressed by subpopulations of T-cells and NKR expression on T-cells has been associated to memory/effector cells (Tarazona et al. 2002, 2004; Vallejo et al. 2004; Abedin et al. 2005; Casado et al. 2005; Delarosa et al. 2006; Michel et al. 2006; Gayoso et al. 2007; Solana et al. 2007; Lemster et al. 2008).

Although NK cells have been considered for many years as being a simple, homogenous and unspecific population in comparison with T- or B cells of adaptive immunity, different subsets have been defined according to the expression of NK markers and their capacity to kill or produce cytokines. Thus, human NK cells can be divided into two functional subsets based on their cell surface density of CD56, $CD56^{bright}$ immunoregulatory cells and $CD56^{dim}$ cytotoxic cells. Both subsets have been characterized extensively regarding their different functions, phenotype, and tissue localization. The $CD56^{bright}$ NK cell subset has a distinctive role in the innate immune response as the primary source of NK cell-derived immunoregulatory cytokines (Cooper et al. 2001; Farag et al. 2003; Wendt et al. 2006). $CD56^{dim}$ and $CD56^{bright}$ subsets also differ in the expression of chemokine receptors that may contribute to cell trafficking (Cooper et al. 2001; Fehniger et al. 2003; Berahovich et al. 2006).

NK cells were long thought to respond directly to tumor or infected cells, but recent data show that NK cells acquire functionality through priming by dendritic cells (DC; Zitvogel et al. 2006; Long 2007; Lucas et al. 2007). This cross-talk between NK cells and myeloid DC also leads to DC maturation and may determine the quality and strength of the adaptive immunity responses (Vitale et al. 2005; Moretta et al. 2006).

NK cells exhibit the capacity to distinguish normal and damaged cells as well as self- and foreign cells. NK cell function is controlled by inhibitory receptors for the MHC class I molecules that are ubiquitously expressed on target cells (Table 1). In consequence, MHC class I positive targets are more resistant to NK mediated lysis. Human receptors for HLA class I molecules can be included into two structural types, those with immunoglobulin (Ig)-type domains (killer Ig-like receptors (KIR) and leukocyte immunoglobulin-like receptor) and those with lectin-like domains called CD94/NKG2 receptors. Inhibitory and activating forms of KIR and CD94/NKG2 receptors have been described. The ligands for KIRs are polymorphic determinants of HLA-A, HLA-B and HLA-C molecules whereas the ligands for the human CD94/NKG2 receptor are complexes of HLA-E bound to peptides derived from the leader sequences of other HLA class I molecules (Borrego et al. 2002; Lopez-Botet et al. 2004; Lanier 2005; Guma et al. 2006). HLA-G, a non-classical MHC class I molecule, is recognized by Leukocyte immunoglobulin-like receptor subfamily B member 1 (LILRB1/LIR1/ILT2/CD85j) and member 2 (LILRB2/LIR2/ILT4/CD85d) and KIR2DL4 (Shiroishi et al. 2006). Inhibitory receptors play a role in "missing-self" recognition, that confers to NK cells the capacity to attack cells that lose or downregulate the expression of MHC class I molecules. However, the expressions of inhibitory receptors on NK cells is not uniform and are germline-encoded by a set of polymorphic genes that segregate independently from MHC genes. Therefore, how NK cell self-tolerance arises in vivo is still poorly understood.

Licensing of NK cells by self-MHC class I has been proposed as a mechanisms for NK cell tolerance to self. This process takes place during NK cell maturation and involves inhibitory receptors that recognize target cell MHC class I molecules. This process results in two types of tolerant NK cells: functionally competent (licensed) NK cells, whose effector responses are inhibited by self-MHC class I molecules through the same receptors that conferred licensing, and functionally incompetent

Table 1 HLA class I specific inhibitory receptors expressed on human peripheral blood NK cells

Receptor	Ligand
KIR2DL1	HLA-C group 2
KIR2DL2/3	HLA-C group 1
KIR3DL1	HLA-B alleles
KIR3DL2	HLA-A alleles
CD94/NKG2A	HLA-E
KIR2DL4	HLA-G
ILT-2/CD85j	HLA-G and other HLA class I molecules
ILT-4/CD85d	HLA-G and other HLA class I molecules

(unlicensed) NK cells. Although this process has been defined for mouse NK cells several findings suggest that human NK cells also undergo this maturation process termed licensing (Kim et al. 2005; Parham 2006; Raulet 2006; Raulet and Vance 2006; Yokoyama and Kim 2006). Once NK cells acquire functional competence through "licensing'' by self-MHC molecules, the result of effector-target interactions is governed by the integration of inhibitory and activating signals that determines whether the NK cell is finally activated, secretes cytokines and lyses target cells (Gasser and Raulet 2006).

NK cells recognize infected cells or tumor cells by using different types of activating receptors (Table 2) that may act in synergy to enhance cytotoxicity or cytokine release after activation (Bryceson et al. 2006). Activating receptors expressed by NK cells include besides the well characterized receptor CD16 that binds FcγRIIIa, NKG2D, CD244, NKp80 and the natural cytotoxicity receptors (NCR) NKp30, NKp46, NKp44. Ligands for activating receptors comprise both non-self ligands and self proteins up-regulated on damaged cells.

The C-type lectin-like receptor NKG2D is unique among activating receptors in that it recognizes a wide range of ligands some of which are primarily expressed in "stressed" tissues or on tumor cells. Human NKG2D ligands are the MHC class I chain related (MIC) proteins MICA and MICB and the UL-16 binding proteins ULBP-1, ULBP-2, ULBP-3 and ULBP-4 (Eagle and Trowsdale 2007; Mistry and O'Callaghan 2007).

NKp30 and NKp46 are constitutively expressed in NK cells and NKp44 is induced after activation (Arnon et al. 2006; Bryceson et al. 2006; Gasser and Raulet 2006). The NKp46 and NKp44 receptors recognize viral haemagglutinins (Draghi et al. 2007; Ho et al. 2008; Cagnano et al. 2008) and NKp30 has been shown to bind a still undefined ligand on DCs. This binding can be inhibited by

Table 2 Activating receptors expressed on human peripheral blood NK cells

Receptor	Ligand
CD16	IgG
NKp30	Unknown
NKp46	Viral haemaglutinin
NKp44*	Viral haemaglutinin
KIR2DS1	HLA-C group 2
KIR2DS2	HLA-C group 1
KIR2DS3	Unknown
KIR3DS1	HLA-Bw4?
CD94/NKG2C	HLA-E
NKG2D	MICA/B, ULBP1-4
CD244 (2B4)	CD48
DNAM-1	CD155, CD112
CRACC	CRACC
NTB-A	NTB-A

* Induced after activation

the main tegument protein of human cytomegalovirus, pp65 (Arnon et al. 2005, 2006).

Along with CD244, that binds CD48, other members of the signaling lymphocytic activating molecule (SLAM) family of NK cell receptors have been identified: NTB-A and CRACC, which bind NTB-A and CRACC, respectively.

Strong stimulatory signaling resulting from increased levels of stimulatory ligands can often overcome inhibitory signals provided by MHC class I molecules expressed on target cells (Bauer et al. 1999; Cerwenka et al. 2000; Diefenbach et al. 2000).

3 Effect of Ageing on NK Cell Number and Kinetics

Several alterations have been described in NK cells with advancing age, both in animals and humans. In old humans, contradictory data exist due mainly to the different selection criteria of the elderly populations studied, a common problem when comparing studies by different research groups. Thus, whereas there are studies showing that overall NK cell number and cytotoxicity is not significantly affected in very healthy elderly people including centenarians, in other studies that have not used the same strict selection criteria, the number or functions of these cells from elderly subjects are decreased (Table 3).

In a recent study it has been shown that ageing has an impact on NK cell kinetics (Zhang et al. 2007). The analysis of NK cell homeostasis using deuterium-enriched glucose has shown that these cells are in a state of dynamic homeostasis consistent with a model of postmitotic maturation preceding circulation and with a turnover time in blood of about 2 weeks. In young healthy individuals the proliferation rate is 4,3±2,4%/day, equivalent to a doubling time of 16 days, the total production rate is $15\pm7\times10^6$ cells/l/day and the half-life is approximately 10 days. However in NK cells from healthy elderly subjects the proliferation and production rates are significantly lower (2,5±1,0%/day and $7,3\pm3,7\times10^6$ cells/l/day, respectively; Zhang et al. 2007). This study demonstrates that NK cell numbers are well preserved in healthy ageing, in spite of evidences for a reduction in total NK cell production rates of about 50%. These results suggest an increased proportion of long-lived NK cells in the elderly subjects. This may be related to the increased proportion of $CD56^{dim}$ cells, as previously reported in elderly subjects (Borrego et al. 1999).

The decreased proliferation and production rates of NK cells in the elderly can be associated to the telomere shortening observed in the elderly. Thus it has been shown that NK lymphocytes show an age-associated loss of telomeres together with an age-associated reduction of telomerase activity that was evident in individuals over 80 years of age in particular in the oldest individuals and in those with increased NK cell numbers (Mariani et al. 2003a, b).

Table 3 Effect of ageing on the NK cell compartment

	Decreased	Preserved	Increased
Percentage of NK cells			Facchini et al. 1987; Mariani et al. 1994; Borrego et al. 1999; Lutz et al. 2005
Number of NK cells			Borrego et al. 1999; Di Lorenzo G. et al. 1999
CD56 dim subset			Krishnaraj 1997; Borrego et al. 1999
CD56 bright subset	Krishnaraj 1997; Borrego et al. 1999		
Perforin content	Rukavina et al. 1998	Mariani et al. 1996	
Cytotoxicity	Facchini et al. 1987; Mariani et al. 1990; Solana and Mariani 2000; Ogata et al. 2001	Sansoni et al. 1993; Kutza and Murasko 1994, 1996	
Intracellular signaling	Mariani et al. 1998a		
ADCC		Sansoni et al. 1993; Mariani et al. 1998a; Solana and Mariani 2000; Plackett et al. 2004; Lutz et al. 2005	
Response to cytokines	Dussault and Miller 1994; Borrego et al. 1999; Murasko and Jiang 2005		
Cytokine and chemokine production	Mariani et al. 2001 2000a, 2000b; Mocchegiani and Malavolta 2004		
In vivo proliferation and production rates	Zhang et al. 2007		

4 NK Cells and Health Status in the Elderly

An extensive analysis of NK cell number and function in elderly individuals strengthens the significance of NK cell activity in healthy ageing and longevity. Thus a decreased NK cell function in old individuals is associated with an increased incidence of infectious diseases and death due to infection in elderly humans (Ogata et al. 1997, 2001) and elderly people (aged >85 years) with low numbers of NK cells were reported to have three times the mortality risk in the first two years of follow-up than those with high NK cell numbers (Remarque and Pawelec 1998). It has been also reported that decreased NK cell activity in the elderly is also associated with increased frequency of disorders as atherosclerosis

(Bruunsgaard et al. 2001). In a similar way it has been shown that a preserved NK function is related to better health status and lower incidence of respiratory tract infections in elderly individuals and to a better response to influenza vaccination (Mysliwska et al. 2004). Additional evidences supporting the significance of NK cells in healthy ageing come from studies in centenarians, that, in general, have a very well preserved NK cell cytotoxicity (Sansoni et al. 1992, 1993; Franceschi et al. 1995). Furthermore, when NK cells are studied in nonagenarians and centenarians the results show that higher NK cell numbers and NK cytolytic activity were associated with better retained ability to maintain an autonomous life style. These parameters were also associated with higher serum vitamin D levels, a well-nourished status and balanced basal metabolism, indicating the impact of hormonal and nutritional variables on NK cell function in elderly people and again emphasizing that results on NK cells may depend to a much greater extent than T-cells on the state of health of the individual (Mariani et al. 1998b; Pawelec et al. 1998). Moreover, the percentage of NK cells has been shown to correlate with serum zinc and selenium concentrations, and with plasma vitamin E and ubiquinone-10 concentrations, confirming that micronutrients may affect the number and function of NK cells in old age (Mariani et al. 1998b; Ravaglia et al. 2000). This suggests that any analysis of biomarkers of immunosenescence must of necessity take these variables into account.

Together, these results support the fact that preserved NK cytotoxicity can be considered a marker of healthy ageing, whereas low NK cytotoxicity is a predictor of increased morbidity and mortality due to infections.

5 Effect of Ageing on the Expression and Function of NK Cell Receptors

Although the overall NK cell cytotoxicity seems not to be significantly affected in the very healthy elderly donors, it has been demonstrated that, even in these donors, there is a decreased cytotoxicity per NK cell, associated with defective signal transduction (Table 3; Mariani et al. 1998a; Solana and Mariani 2000). Thus, the maintenance of NK cell activity is probably due to a compensatory increase in the number of NK cells to accommodate a possible decrement of NK cell cytotoxicity (Mariani et al. 1994). This increased cell number has been related to a higher number of $CD56^{dim}$ rather than $CD56^{bright}$ subset containing the most cytotoxic NK cells (Borrego et al. 1999; Solana et al. 1999). Neither the binding of effector cells to the target cells nor the perforin content of NK cells is significantly different in the old and young groups. On the contrary the defective NK cell cytotoxicity is associated with a decreased capacity of NK cells to release IP3 after interacting with the target cells and a delayed hydrolysis of PIP2, indicating that the PKC-dependent pathway is affected as a consequence of ageing (Mariani et al. 1998a). However NK activation and cytotoxic granule release induced by CD16 crosslinking is not affected by ageing (Pawelec et al. 1998; Solana et al. 1999; Solana and Mariani 2000; Bruunsgaard et al. 2001; Lutz et al. 2005).

Furthermore the PI-3-kinase pathway coupled to CD16 triggering is not significantly affected in NK cells from elderly people, indicating that the transduction pathways involved in natural or CD16-dependent NK cytotoxicity are differentially affected by ageing (Mariani et al. 1998a; Solana and Mariani 2000).

Despite the maintenance of CD16-mediated killing, the decreased per-cell NK cytotoxicity against the classic target cell line K562 suggests that the expression and/or the functionality of other NK activating receptors are likely to be defective in the elderly. Very little is known about the effects of senescence on the function of NK receptors, and discrepant results have been reported in this context. Whereas it was reported that the expression of HLA-specific killer immunoglobulin-like receptors is not significantly affected in NK cells from elderly compared to young donors (Mariani et al. 1994), other study has shown that NK cells present an age-related increase in KIR expression and a reciprocal decrease in CD94/NKG2A expression, although the CD94/NKG2A inhibitory signaling pathway is intact (Lutz et al. 2005).

In relation with the expression of other NK receptors involved in NK cell cytotoxicity, our results show that NK cells from elderly donors have a decreased expression of the activating receptor NKp30 (Fig. 1). NKp30 mediates the crosstalk between NK and DCs via the recognition of an unknown ligand expressed on DCs. As summarized on Figure 1 the engagement of the NKp30 receptor can lead either to a direct killing of DCs by NK cells, or to the secretion of IFN-gamma and TNF-alpha and the subsequent maturation of DCs. Therefore NK-activated DCs loaded with tumor or virally derived antigen have an increased capacity to prime T-cells. In return, activated DCs release Th1 cytokines that further enhances NK activation (Arnon et al. 2005, 2006). The decreased expression of this receptor on NK cells

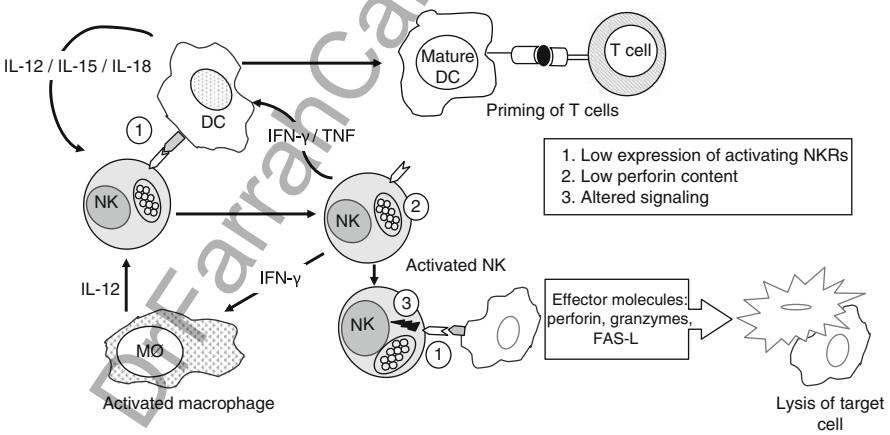

Fig. 1 Effect of human ageing on NK cell function. Cross-talk of NK cells with DCs through NKp30 receptor interaction with its unknown ligand results in inducing DCs maturation and NK cell activation. Whereas DCs collaborate with T-cells in the initiation of adaptive response, activated NK cells produce cytokines and kill target cells. Age-associated alterations in NK cell include: (1) Low expression of activating NKRs that could result in defective cross-talk with dendritic cells and defective recognition of target cells, (2) low perforin content, and (3) altered signal transduction

from elderly individuals should also affect the interaction between these cells leading to a decreased capacity to collaborate in the initiation of the adaptive immune response against virus infected or tumor cells (Fig. 1).

6 Effect of Ageing on NK Cell Response to Cytokines

Cytokine activation of NK cells results in enhanced cytotoxicity and in the synthesis and release of cytokines and chemokines. The enhancement of the cytotoxic activity of NK cells in response to IL-2, IL-12 or IFN-α and γ is well preserved in the healthy elderly. However, the capacity of these cytokine-activated killer cells to lyse the NK-resistant Daudi cell line is significantly decreased in the elderly (Kutza and Murasko 1994, 1996; Murasko and Jiang 2005). A major effect of ageing on cytokine and chemokine production by NK cells is a marked early decrease in IFN-γ secretion in response to IL-2, which can be overcome by increasing the incubation time (Murasko and Jiang 2005). In a similar way the production of MIP-1α, Rantes

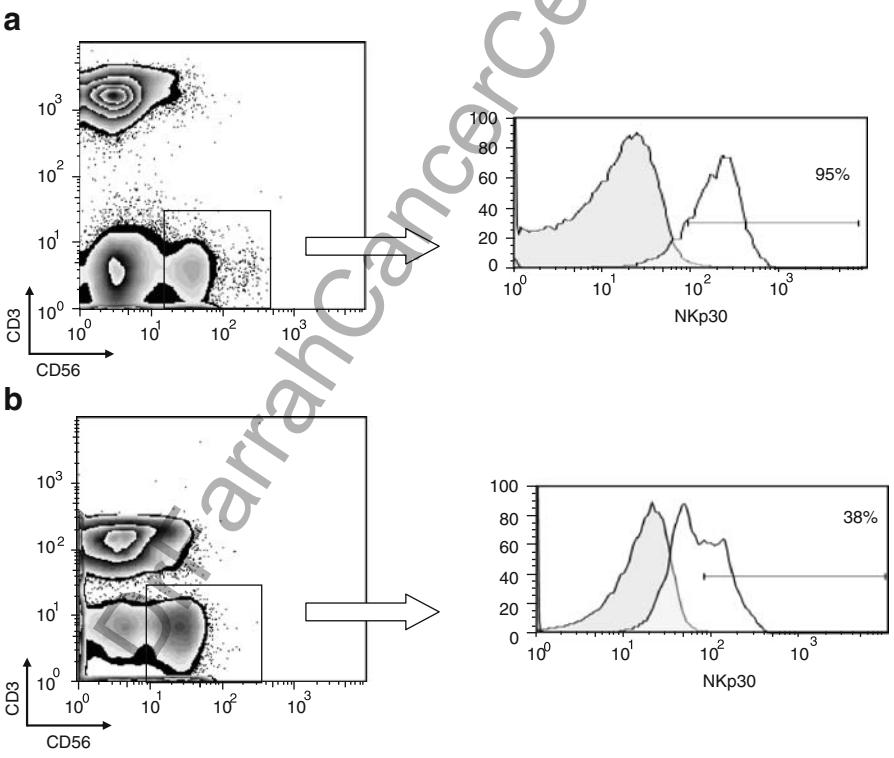

Fig. 2 Expression of NKp30 on NK cells from healthy young (a) and elderly (b) individuals. Peripheral blood lymphocytes were labeled with monoclonal antibodies against CD3, CD56 and NKp30. Results were analysed with a FACSCanto cytometer. Reduction of percentage and mean fluorescence channel of NKp30 was observed in elderly individuals

and IL-8 chemotactic cytokines by NK cells is decreased both in elderly subjects in response to IL-2 and in nonagenarians in response to IL-2 or IL-12 although these cells express the corresponding chemokine receptors. Because of the co-stimulatory role of chemokines on NK cell responses, the decreased production of chemokines can be involved in the defective functional activity of NK cells from old subjects (Mariani et al. 2001, 2002a, b).

Ageing also affects the response of NK cells to IFN-α/β both in mice and humans. This decreased response could be related to the delay in virus clearance observed in aged mice (Murasko and Jiang 2005). These results suggest that NK cells do show an age-associated defect in their response to cytokines, with a subsequent detriment both in their capacity to kill target cells and synthesize cytokines and chemokines.

7 Conclusions and Perspectives

NK cells are a key component of innate immunity in the elimination of virus infected or tumor cells. Recent evidences also support their significance in the initiation of adaptive responses by their crosstalk with DCs and subsequent activation of T-cells. NK cells can be affected by ageing, although several studies have shown a good correlation between the number and/or function of NK cells and the maintenance of an adequate health status in elderly and very elderly people (including nonagenarians and centenarians). On the contrary a decreased NK cell function is associated to increased risk of infectious diseases and risk of death due to infections, supporting the importance of the altered functions of NK cells in the age-associated deterioration of the immune system called immunosenescence.

Our recent finding that NK cells from healthy elderly individuals have a decreased expression of NKp30 receptor, important not only in NK cytotoxicity but also in regulating their cross-talk with DCs strongly support that the alterations in NK cells by ageing may have important consequences that may help to explain the association between a preserved NK cell function and the maintenance of a healthy status. Further studies on the effect of ageing on all NK cell subsets, on the expression and function of activating and inhibitory receptors and a more profound study of the molecular mechanisms involved in these processes are required to better understand the contribution of NK cell ageing to immunosenescence. Considering the increasing advances in the understanding of the mechanisms involved in NK cell interactions not only with tumor and virus infected target cells but also with other cells of the immune system the analysis of how ageing affect these different processes is mandatory.

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