Virus Research 157 (2011) 128–133

Contents lists available at ScienceDirect

Virus Research

journal homepage: www.elsevier.com/locate/virusres

Intrinsic cellular defense mechanisms targeting human cytomegalovirus

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ARTICLE INFO

Article history:
Available online 8 October 2010

Keywords:
HCMV
Nuclear domain 10
PML nuclear bodies
PML
Sp100
hDaxx
ATRX
Antiviral defense
Intrinsic immunity

ABSTRACT

In recent studies we and others have identified the cellular proteins PML, hDaxx, Sp100 and ATRX, which form a subnuclear structure known as nuclear domain 10 (ND10) or PML nuclear bodies (PML-NBs), as host restriction factors that counteract cytomegalovirus infections by inhibiting the initiation of viral immediate-early (IE) gene expression. The antiviral function of ND10, however, is antagonized by viral regulatory proteins which either induce a proteasomal degradation of ND10 proteins or a disruption of the subnuclear structure. This review will summarize our current knowledge on the inhibition of cytomegalovirus replication by ND10 proteins. Furthermore, viral strategies to defeat this host defense mechanism are discussed.

1. Intrinsic immunity of the cell

The mammalian immune system has evolved under continuous selective pressure from the wide range of microorganisms it was exposed to for millions of years. Only recently, intrinsic cellular-based defense mechanisms which give cells the capacity to resist pathogens have been discovered as an essential component of immunity giving rise to a third branch of the traditionally bipartite immune system of innate and adaptive immunity. Innate immune mechanisms largely depend on recognition of pathogens by specific cellular receptors (e.g. toll-like receptors) which sense common pathogen-associated molecular patterns (PAMPs) to elicit broad defensive responses mediated by cytokines, macrophages and natural killer cells, while adaptive immunity is a collective term for the long-lasting and specific response of lymphocytes to pathogen-derived antigens (Roy and Mocarski, 2007). Unlike the innate and adaptive part of the immune system, that require pathogen-induced signaling cascades in order to be turned on, intrinsic immune defenses are mediated by cellular restriction factors that are constitutively expressed and active even before a pathogen enters the cell, thus illustrating the first line of defense (Bieniasz, 2004). However, an interplay between innate and intrinsic immune mechanisms has been demonstrated: in particular, it was shown that several cellular restriction factors can be upregulated by interferon treatment thus enhancing their antiviral activity (Tanaka et al., 2006; Lavau et al., 1995; Sakuma et al., 2007). Further characteristics of intrinsic immune mechanisms are that they are saturable and subject to pathogen-based countermeasures.

Components of the intrinsic immunity have first been identified in the context of viral infections when it became apparent that cellular host factors like APOBEC enzymes or the tripartite motif protein TRIM5α have the potential to confer resistance to retroviral infections and by this may affect viral tropism (Mangeat et al., 2003; Stremlau et al., 2004). The exact mode of action of these cellular factors with regard to the restriction of retroviral replication or also the movement of mobile genetic elements as well as the various countermeasures viruses have evolved to this have extensively been reviewed in recent publications (Takeuchi and Matano, 2008; Goila-Gaur and Strebel, 2008). Thus, in this article we concentrate on the very recent finding that herpesviruses are also subject to intrinsic immune responses mediated by cellular restriction factors like ATRX, hDaxx, PML or Sp100 (Tavalai and Stamminger, 2009). Interestingly, all these factors have been found to be constituents of a cellular, subnuclear structure known as nuclear domain 10 (ND10) giving rise to the idea that ND10 are part of an antiviral defense mechanism of the cell.

2. The subnuclear structure ND10

Nuclear domains 10 (ND10), also referred to as PML nuclear bodies (PML-NBs), or PML oncogenic domains (PODs), are dynamic, spherical, macromolecular structures that are defined by the presence of the major components PML, hDaxx, and Sp100 which accumulate in distinct foci within the interchromosomal space of

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doi:10.1016/j.virusres.2010.10.002

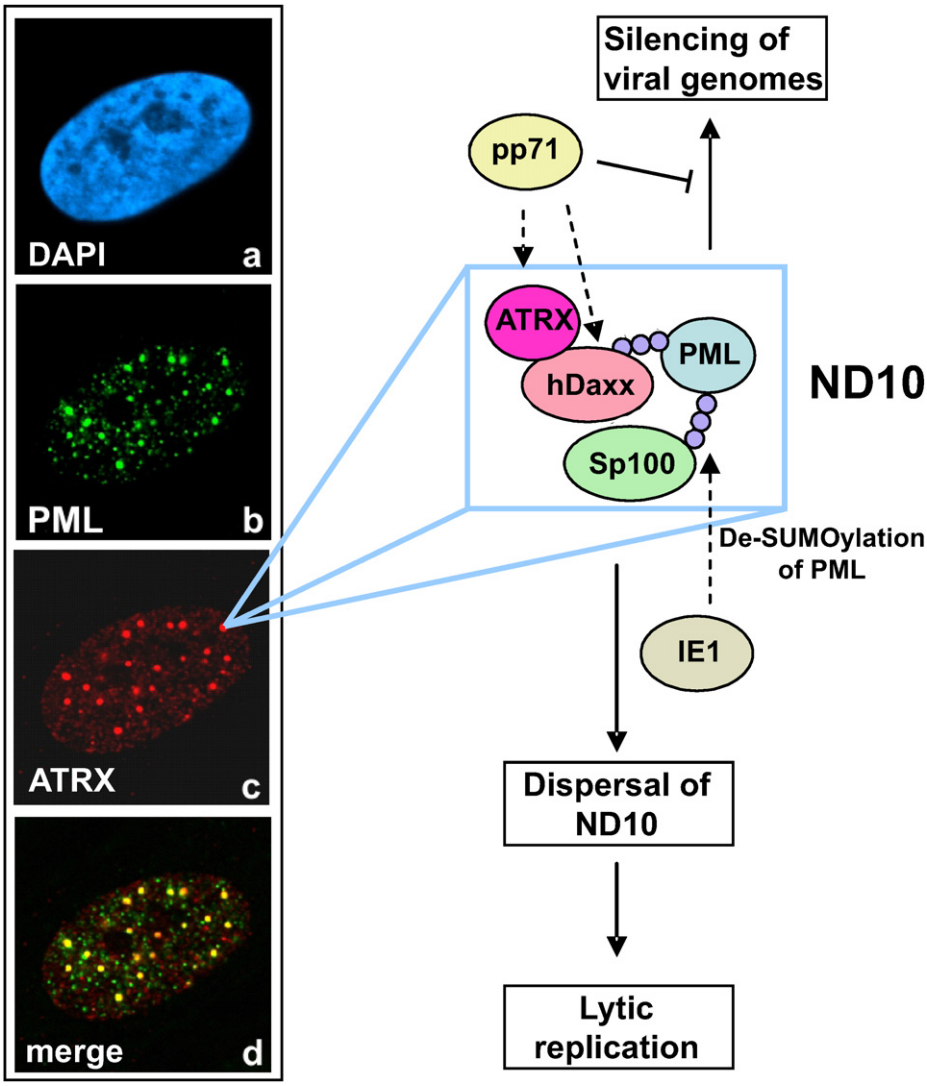

Fig. 1. Visualization of ND10 by immunofluorescence detection of PML and ATRX in primary human fibroblast cells and model of ND10 modification by the cytomegaloviral antagonistic proteins pp71 and IE1. The left panel of the figure visualizes the subnuclear structure ND10 by costaining of primary human fibroblast cells with antibodies directed against PML (b) or ATRX (c) followed by immunofluorescence detection using confocal microscopy. Subpanel a shows the cell nucleus as detected by DAPI staining; subpanel d is a merge of the PML and ATRX staining, thus demonstrating the colocalization of both proteins in ND10. The scheme in the right part of the figure illustrates a simplified model of the protein composition of ND10, showing the major ND10 proteins PML, hDaxx and Sp100 as well as the chromatin remodeling factor ATRX. Furthermore, the targeting of specific ND10 factors by the viral proteins pp71 and IE1 is indicated, which antagonizes the ND10-mediated silencing of viral genomes, thus resulting in lytic viral replication.

the nucleus (Bernardi and Pandolfi, 2007; Lallemand-Breitenbach and de The, 2010) (Fig. 1). The PML protein illustrates the key organizer of ND10 as it is responsible for the recruitment of an ever-growing list of proteins to this matrix-associated structure, whose only common feature seems to be their ability to be posttranslationally modified by SUMO (Van Damme et al., 2010). The enrichment of SUMOylatable proteins at ND10 as well as the observation that, in principle, all components of the SUMO conjugation pathway are present at this subnuclear structure fostered the hypothesis that ND10 may function as a nuclear hotspot for SUMOylation (Van Damme et al., 2010). In fact, both covalent as well as non-covalent SUMO interactions are regarded to constitute the basis for PML-body formation since only SUMOylated PML is capable of assembling ND10 structures (Lallemand-Breitenbach et al., 2001; Shen et al., 2006; Zhong et al., 2000a,b; Ishov et al., 1999). In addition, ND10 have been implicated in the regulation of diverse cellular key processes like oncogenesis (Salomoni and Pandolfi, 2002), DNA damage repair (Dellaire and Bazett-Jones, 2004), apoptosis (Takahashi et al., 2004; Bernardi et al., 2008), stress response (Maul et al., 1995), senescence (Bischof et al., 2002) as well as the regulation of gene expression (Zhong et al., 2000b). Interestingly, evidence is accumulating that ND10 are also involved in antiviral defense due to their protective role against many viral infections (Tavalai and Stamminger, 2008), including herpesviruses which have been most extensively studied in this respect (Everett and Chelbi-Alix, 2007; Tavalai and Stamminger, 2009). The aim of this review is to briefly summarize the current state of knowledge concerning the contribution of ND10 constituents to the intrinsic immune defense against human cytomegalovirus (HCMV) infections, a β-herpesvirus whose study contributed substantially to the view of ND10 as part of an antiviral host response.

3. Restriction of HCMV replication by the subnuclear structure ND10

Since the discovery of ND10 as sites of HCMV input DNA deposition, which has been made approximately 15 years ago, the functional significance of this finding for viral replication has been