Kallikrein-6—Regulated Pathways Shed Light on New Potential Targets in Varicella Zoster Virus Infection

Stephan M. Caucheteux1 and Vincent Piguet1,2

Varicella zoster virus, the worldwide infectious human virus responsible for acute varicella and chickenpox, commonly spreads from exposure through contact with a skin lesion or airborne respiratory droplets. Keratinocytes, major targets and source of transmission of the virus present in the skin, represent an ideal choice of cell to stop early virus progression. In their recent study, Tommasi et al. show regulatory mechanisms of cytokeratin 10 through the protease kallikrein-6 as a suitable and druggable pathway to reduce varicella zoster virus dissemination.


1Division of Dermatology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada; and 2Division of Dermatology, Women’s College Hospital, Toronto, Ontario, Canada

Correspondence: Vincent Piguet, Division of Dermatology, Department of Medicine, Women’s College Hospital, 76 Grenville Street, Toronto, Ontario M5S 1B2, Canada. E-mail: vincent.piguet@utoronto.ca

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be available, and a recombinant zoster vaccine (Shingrix) has been an alternative since 2017. Although the newer vaccines and current antiviral drugs efficiently prevent shingles and postherpetic neuralgia and reduce their risk of development by approximately 90%, the development of alternative therapies that limit establishment of a latent VZV reservoir is necessary to prevent these complications. The main targets of VZV are T lymphocytes, epithelial cells, and ganglia. The initial infection will trigger chickenpox, whereas its latency in ganglionic neurons will be responsible for shingles once the virus becomes active again. The major source of infectious virus is found in skin cells and will spread as shedding skin vesicles and cell-free virus (Chen et al., 2004).

In their recent study to further understand the regulation of VZV infection and identify new potential targets, Tommasi et al. (2019) show that upregulation of the protease kallikrein-6 (KLK6) during VZV infection in keratinocytes induces cytokeratin 10 (K10) ubiquitination by MDM2. Notably, preventing K10 degradation in vitro reduced VZV propagation.

VZV skin tropism is highly dependent on polykaryocyte formation. Playing a critical role in the induction of antiviral immunity, several major types of dendritic cells (DCs) have been found to contribute to the initiation of immune responses in skin. Among DC subtypes, an increase of plasmacytoid DC infiltrates into dermal VZV lesions was observed as well as a dramatic decrease in IL-12-producing CD1a+ DC and Langerhans cells in the epidermis (Gutziet et al., 2010).

Initial host defenses are mediated by innate immune responses involving natural killer cells and type 1 interferons, and VZV viral replication is ultimately controlled by adaptive immune responses (Arvin et al., 1986; Gershon and Steinberg, 1979; Kim et al., 2017; Tilden et al., 1986). In particular, anti-VZV glycoprotein gE T helper type 1 immunity is essential for control of the viremic phase with contributions by IgM, IgA, and IgG antibodies that are directed against a wide range of VZV proteins (Hayward et al., 1991).

High epidermal viral replication will ultimately result in skin lesions, leading to formation of cutaneous vesicles that are filled with clear fluid containing infectious VZV particles. After resolution of initial infections, latent VZV virus can persist lifelong in sensory ganglia, retaining the ability to replicate and boost VZV-specific T-cell memory. The decrease in VZV memory T cells that is associated with aging is likely to contribute to the increased occurrence of VZV-associated pathologies in individuals over 50 years of age (Vukmanovic-Stejic et al., 2015). RNA sequencing analysis showed that VZV infection has a dramatic effect on keratinocytes, decreasing the expression of cytokeratins and compromising epidermal structures—a phenotype that shares similarities with skin aging (Jones et al., 2014).

In their study, Tommasi et al. (2019) analyzed the mechanisms of regulation of K10 in differentiated keratinocytes and in skin explants infected with VZV. The study shows that KLK6 expression is increased in VZV-infected skin. This leads to an upregulation of K10 ubiquitination by MDM2 and subsequently to its degradation, contributing to the structural disruption of the epidermis and the induction of syncytia. Finally, NR4A1 is upregulated, enhancing VZV propagation, stimulating autophagy but decreasing lysosome function.

Tommasi et al. (2019) identify the KLK6 pathway as a potentially new druggable target with inhibitors of ubiquitin-ligase MDM2, K10, or NR4A1 to prevent VZV cutaneous replication and long-term complications associated with VZV infection.