Topic: VIRAL IMMUNOLOGY AND VACCINES

Title: VIRUS-INDUCED CITRULLINATION AS A STRATEGY TO SUBVERT THE HOST'S INNATE ANTIVIRAL DEFENCE

Author:
V. Dell'Oste[1]

Affiliation:
[1]Department of Public Health and Pediatric Sciences, University of Turin, Turin, Italy

Diverse host and virus-mediated post-translational modifications (PTMs) have been shown to take part in many aspects of viral pathogenesis. The action of the most prevalent PTMs, encompassing phosphorylation, glycosylation, acetylation, methylation, and ubiquitination is well documented. Citrullination, also called deamination, is a less explored PTM catalyzed by protein arginine deiminases (PADs), which convert peptidyl-arginine into peptidyl-citrulline. The PAD family in humans consists of five isozymes (PADs 1-4 and 6), expressed across various tissues. Accumulating evidence indicates that PAD dysregulation is strongly implicated in the pathogenesis of various diseases, including autoimmune conditions, neurodegenerative disorders, and cancer.

A direct correlation between citrullination and viral infections has only recently been established. In this context, our group has unveiled the role of citrullination in promoting human cytomegalovirus (HCMV) and herpes simplex virus 1 (HSV-1) infection through the deimination of several cellular proteins, thereby enhancing viral fitness. Notably, interferon-inducible proteins, including IFIT1, IFIT2, and Mx1, which are highly expressed during the antiviral immune response, were found to be citrullinated during infection. Furthermore, we have shown that a new class of host-targeting antivirals (HTAs) inhibiting PADs exhibits a marked antiviral activity.

PADs are also involved in human epidermal keratinization and morphogenesis as well as skin tumorigenesis, processes closely linked to human papillomaviruses (HPVs) transformation. Our findings revealed that PAD-mediated protein citrullination significantly contributes to HPV-driven epithelial cell transformation. Specifically, both total protein citrullination and PAD4 expression levels are significantly associated with cervical cancer progression. Epithelial immunostaining for PAD4 revealed an increasingly higher histoscore from low-grade (CIN1) to high-grade (CIN2, CIN3) cervical intraepithelial neoplasia and invasive squamous cell carcinoma (SCC) lesions. This raises the possibility that PADs could be promising targets for developing new HTAs to prevent HPV-related cancer progression.

Overall, our research points to a crucial role of citrullination in subverting cellular responses to viral infection and demonstrates that PAD inhibitors efficiently suppress infection *in vitro*, providing a strong rationale for their repurposing as antiviral drugs.