Pathology Elsewhere

SPICE: *Variola* virus virulence factor and potential target for therapy

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The possible re-emergence of *Variola* virus, the causative agent of smallpox, as a potential bioterrorism agent has led to renewed interest in the pathogenesis of smallpox and in the development of therapies and safer vaccines. *Variola* virus, as the most virulent member of orthopoxviruses, specifically infects humans and has no other animal reservoir. As smallpox was eradicated before techniques for the manipulation of DNA were widely available, very few molecular studies of this virus are available, and the *Variola* virus itself, its genomic DNA and its proteins are not available to the general scientific community. Another orthopoxvirus, *Vaccinia*, shares remarkable DNA homology, and was used in the global eradication of smallpox, which ended in the late 1970s.

Among many proteins encoded by *Variola* virus, over 80 are located in the terminal regions of the genome, where proteins associated with host immune evasion¹ are encoded. To date, only two *Variola* proteins have been characterized: smallpox inhibitor of complement enzymes (SPICE) and a high-affinity secreted chemokine-binding protein type II.

A recent paper published in the *Proceedings of the National Academy of Sciences* has demonstrated a molecular approach to engineer SPICE, a homologue of a *Vaccinia* virulence factor, *Vaccinia* virus complement control protein (VCP). SPICE coding sequence was generated from that of VCP by site-directed mutagenesis, and recombinant SPICE and VCO were produced in mammalian and insect cells and affinity purified. SPICE and VCP demonstrate a preference for complement from different species in hemolytic experiments. SPICE efficiently prevents the stabilization of human C3b and C4b, inactivates the convertases, and consequently decreases the production of inflammatory mediators C3a, C4a, and C5a. Furthermore, SPICE is nearly 100-fold more potent than VCP at inactivating human C3b and six-fold more potent at inactivating C4b, and is also more human-specific than VCP.

‘Assuming that complement is as critical to orthopoxvirus containment in humans as it is in rodents, SPICE seems to be a virulence factor for *Variola* virus’, said Ariella Rosengard,² the principal investigator of the research. Disabling

SPICE could represent an approach for the treatment of smallpox, and disabling VCP could represent an approach for the development of a safer smallpox vaccine.

These studies help to understand the pathogenesis of smallpox and may also assist in the development of targeted therapies for the treatment of smallpox.

References

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TIMP-2 inhibits angiogenesis, independent of MMP mechanism

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The matrix metalloproteinases (MMPs) are a family of more than 20 distinct zinc endopeptidases that are frequently overexpressed in human tumors. These enzymes have been shown to play an important role in the proteolytic destruction of extracellular matrix and basement membranes. The remodeling of extracellular matrix is critical for neoplastic cell proliferation and angiogenesis, and ultimately facilitates tumor invasion and metastasis. In nonpathogenic conditions, MMP proteolytic activity is precisely regulated by the tissue inhibitors of metalloproteinases (TIMPs). Owing to the relevance of MMPs in tumor progression, a number of different strategies have been developed to block the unwanted activity of these enzymes in cancer. Unfortunately, most clinical trials with the first series of MMP inhibitors have failed to show clear benefits to patients with advanced cancer.

It is now widely appreciated that TIMPs have pluripotential effects on cell growth, apoptosis, and differentiation in addition to their MMP inhibitory activity. A newly published study in *Cell*¹ demonstrated that TIMP-2 and Ala+TIMP-2 potently inhibit endothelial cell proliferation in response to FGF-2 or VEGF-A stimulation *in vitro*. *In vivo*, TIMP-2 and ALA+TIMP-2 potently inhibit angiogenic responses induced by either FGF-2 or