C.114- Highly pathogenic Influenza virus A H5N1 (Vietnam, Hong Kong) polymerase PB2 contains a snake disintegrin homologous to platelet integrin ITGA2b (gpIIb), which blocks the formation of platelet clot.

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Avian Influenza virus A H5N1 is compared to chicken Ebola as its symptomatology is characterized by a massive internal hemorrhage. We have found in Influenza virus an urokinase-plasminogen activator and an epitope FP on the platelet surface integrin gpIIIa (ITGB3) inducing auto-antibodies against platelets ; here we focus on the hemorragin (hemorragic protein) from Crotalidae, Viperidae and australian Elapidae snakes, called also disintegrin (flavostatin, flavoviridin, trimestatin, echistatin gamma, applagin, ML-6,9,10) which contain a RGD adhesion motif, homologous to the RGN of platelet integrin ITGA2b. Disintegrin inhibits platelet aggregation induced by ADP, thrombin, collagen, arachidonic acid and thromboxan A2. By comparing ITGA2b, snake disintegrin to Influenza virus H5N1 (Hong Kong/Vietnam) polymerase PB2, we found an alignment centered on RGD: ITGA2b 723-PMKKNAQI GIaML V S VGN-740

Influenza 48-(P,V)KaaRGQYSGF-VR(L,T)FQQ-65

ITGA2b 741-LEEAG(S,E)VSFQLQIRSKNSQNPNSKIVLLDVPVRAEA-777

Influenza 66-MRDVLGT(D,F)TVQIIKLLLPFAA(K,P)QSRMQFSSLT(N,V)VRGSG-106

Disintegrin 412-VEEcDcGSPSNPSNPccD/KFPLc/RPgaQcaSgLccDQcRFMKEGTI-454

ITGA2b 778-QVELRGNSFPASLVV-792

Influenza 108-MRILVRGNS-PAFNYN(A,K)T-125

Disintegrin 455-CRIARGD-FPD-DYcNG K T-472

Despite the absence of any cysteine in ITGA2b and Influenza, the alignment could be done with disintegrin (13 cysteines, all gapped). Conclusion : The strategy of snake and Influenza virus is to mimic platelet integrin ITGA2b (gpIIb), particularly at the adhesion motif 783-RGNSFP-788, to block the aggregation of platelets and impede the formation of the platelet clot. Theoretically, a drug designed to mimic RGD by cyclisation (cycloRGD) would block the disintegrin. As the perturbation of coagulation in hemorragic Influenza is complex (fibrinolysis, auto-immune thrombocytopenia), the therapeutic approach must be a combination of plasminogen activator inhibitor, FP peptidomimetics, cycloRGD and heparin (Calciparin was efficient in a DIC induced by a Crotalus viridis bite, and also in Marburg). Whether selenium could be efficient, as it is in Haantan virus hemorragic fever, must be tried in Influenza. Ligands of the Na+ voltage-gated channel may be useful. Intriguingly, the Bost-Blalock theorem was confirmed in the case of RGD (ITGA2b) binding to FPVS (ITGB3).