Equine influenza virus epigenetically imprints airway basal cells and alters chronically the airway epithelium repair potential

Caroline Chauche, The University of Edinburgh, UK
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Equine influenza virus (EIV) is an important respiratory pathogen that causes a severe disease in horses and poses a constant and serious threat to the welfare of racehorses. EIV infects cells in the horse lung and causes their death, creating microscopic holes in the process that needs to be promptly repaired. If this repair is deficient, the horse will take longer to recover, and its lungs might get permanently damaged. Identifying a dysfunctional lung repair response in a young racehorse exposed to flu is essential to better protect it and avoid long-term lung damage.

EIV infects different cells in the lung, and notably some called respiratory basal cells, whose role is to repair the lung after injury. They are instructed to do so by repair molecules that make them multiply and transform into other lung cell types that EIV has just destroyed. Interestingly, the repair molecules are also involved in initiating the production of defence molecules responsible for alerting the body that it is infected by a virus. To fight back and stay in the body, EIV produces a camouflage molecule, whose function is to prevent the defence molecules to be produced. Scientific information obtained in mouse and human indicates that the camouflage molecule can do so by manipulating the host genome in infected cells. Furthermore, when the flu virus infects respiratory basal cells in the mouse it blocks the repair molecules, which inhibits the production of the defence molecules, but also prevents the repair of the damaged lung. To date, it is unknown if the camouflage molecule of EIV can modify the horse genome, or if EIV can block the repair molecules to prevent the defence molecules to be produced.

To demonstrate that the EIV camouflage molecule can modify the horse genome of infected cells and block the repair molecules, I will infect horse respiratory basal cells in the laboratory with normal EIV and EIV that lacks the camouflage molecule and study the cell genome. I will then enable these basal cells to develop into mature lung cells - as it happens during lung repair - and evaluate if these new lung cells are also abnormal genetically.

Equine flu is a huge welfare and economic burden for the Thoroughbred and the equine industry, and my goal is to alleviate it by providing a technique that detects manipulation of the horse genome by EIV in the cells that are responsible for repairing the lung. Understanding how a dysfunctional repair response leads to long-term alteration of the horse lung is an essential step towards the design of an evidence-based assessment protocol of lung repair that can be applied to young racehorses exposed to flu. It has also the potential to directly lead to the development of novel therapeutics to promote healthy lung repair and guarantee prompt and safe return to training and racing activities. Developing such novel knowledge would have a significant positive impact for both the welfare and long-term athletic career of Thoroughbreds, world-wide.