

## Learning Group 08 (Task 4)

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| <b>Title</b>                         | <b>PH-Gradient of the endosomal apparatus</b>   |
| <b>Introduction/<br/>Description</b> | Ionophores can be used to make channels in membranes that allow proton exchange, and thus lead to the destruction of the pH gradient across cellular membranes. Upon ionophore treatment, the luminal endosomal pH across the endosomal pathway is equilibrated with buffered neutral extracellular pH (for example pH 7.2) within minutes. |
| <b>Question</b>                      | What are the possible consequences?   |

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| <b>Choice 1</b> | Because of the neutral pH-value, a virus like SFV cannot be triggered to undergo the conformational change to the fusion competent state to penetrate the endosomal membrane. |
| <b>Choice 2</b> | The EGFR signaling pathway is constitutively active, because although the increase in pH doesn't affect the trafficking of EGFR to the LE, it inhibits its recycling.         |
| <b>Choice 3</b> | The endosomal uptake of iron via transferrin is impaired, because of a disruption in the electrochemical gradient of the plasma membrane due to ionophores.                   |
| <b>Choice 4</b> | Due to the neutral pH, lysosomal hydrolases will lose their regulation and start degrading the endosome itself, leading to an overall cell damage.                            |

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| Feedback Choice 1 | (CORRECT) Viruses like SFV depend also on the pH cue of endosomes, which triggers specific fusion proteins to find a new thermodynamically-favorable state, known as a metastable state transition. The fusion proteins reorganize from hetero-dimers with the virus receptor to homo-trimers. The homo-trimers extend and expose the fusion peptide, which inserts into proximal membrane allowing penetration, followed by uncoating and ultimately release the viral genome.   |
| Feedback Choice 2 | (INCORRECT) The recycling of EGFR is not dependent on pH, and EGFR is able to cycle from plasma membrane to an endosomal compartment and return to the plasma membrane. The signal to sequester EGFR into an intraluminal vesicle targeted to the lysosome depends on the EGFR ubiquitination status at the plasma membrane. Both recycling and Ub-mediated targeting can occur with neutral endosomal pH. However, without acidic pH condition, the function of late endosomes and lysosomes is dysregulated and degradation does not occur. |
| Feedback Choice 3 | (INCORRECT) Fe <sup>2+</sup> binding to Transferrin (Tfn) is pH dependent. Extracellular Tfn binds two Fe <sup>2+</sup> at neutral pH at the plasma membrane, and can be internalized via clathrin-mediated endocytosis. The iron is released in the early endosome due to its acidic pH. Therefore, iron binding and release is influenced by pH, and the difference in pH between the extracellular space and endosomes is used to create directional transport.  |
| Feedback Choice 4 | (INCORRECT) Acidic environment increases the activity of lysosomal enzymes (eg. hydrolases). An increase in pH would cause those enzymes to have a lower activity. Also, proteins and lipids at the limiting membrane of lysosomes are resistant to the hydrolases of the lysosomes due in part to strong glycosylation.  |