Scottish Government Health Directorates Chief Scientist Office

CHIEF SCIENTIST OFFICE

FOCUS ON RESEARCH

DEFINING THE FUNCTIONAL ROLE OF NOVEL MHC CLASS I DIMERS ON SECRETED EXOSOME VESICLES

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Aim
To determine the function of a novel form of an immune protein called major histcompatibility complex (MHC) class I molecules, when found on biological droplets called exosomes released by cells.

Project Outline/Methodology
MHC class I molecules are key proteins of the human immune system, because they allow the detection and elimination of cells infected with viruses. MHC class I molecules are normally found on the surface of healthy cells, however, recently we also discovered them on the surface of small droplets released from cells, called exosomes. On exosomes, two MHC class I molecules are often stuck together to form a novel structure. Here, we used immunological techniques to determine whether the presence of single or double MHC class I molecules cause the exosomes carrying them to behave differently. This will help us understand the role these droplets play in the immune system.

Key Results
Immune white blood cells release similar amounts of several bioactive chemicals called cytokines when stimulated with both versions of the MHC class I protein on exosomes. However, when exosomes with the double version of the MHC class I protein alone were used we detected differences in the secretion of eight other cytokines, including many that are released during the onset of inflammation during an infection. Interestingly, when MHC class I molecules were absent from exosomes, we noted the release of a cytokine that can inhibit the function of normal immune cells.

Conclusions
The normal role of MHC class I proteins does not appear to be altered when exosomes express both the single and the double form of MHC class I protein. However, the double form alone stimulates the release of a number of cytokines indicative of early inflammation.

What does this study add to the field?
The activity of MHC class I molecules on exosomes has not been studied in detail. Our data suggests that they behave normally, as they would on healthy cells. In contrast we discovered that when very few or no MHC class I molecules are present, large amounts of an immunosuppressive cytokine can be released. This may have uncovered a novel immune evasion strategy, as many tumours lose MHC class I molecules. Releasing exosomes with few or no MHC class I may cause the local release of inhibitory cytokines that prevent immune cells from attacking the tumour.

Implications for Practice or Policy
Exosomes have already been tested in Phase I clinical trials to try to boost immune responses to cancers. However, we understand relatively little about how the exosomes influence the immune system. We have started to investigate this process by studying the behaviour of immune cells when exosomes are added. Our initial data suggests that exosomes with low levels or no MHC class I proteins could prove problematic and should be avoided.

Where to next?
We have applied for further research council grant funding to extend the cytokine observations made here.

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