

The juice of life

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There is no life without blood. Pumped through us by the heart, blood carries the oxygen we breathe and relays it to every part of our body to keep us going. If too much of it leaves us, life leaves us too. As a consequence, this rich red fluid has become a powerful social, religious and literary symbol. Our bodies also know how vital it is and produce red blood cells continuously to replace those that have gone past their use-by date. However, there are instances – an accident, an illness or surgery for example – when the amount of blood required exceeds the amount that a body can produce on its own. And the only way to solve the problem is by pouring fresh blood into the body which needs it. It sounds simple but it is not. Today we know that blood can only be transfused if both the donor's and the recipient's blood match. If they don't, our immune system will eventually kill us. Blood is always difficult to come by so years of research have been dedicated to finding ways of making it. Recently, a couple of bacterial enzymes were discovered, which could 'clean' red blood cells so that they could be transfused to any patient regardless of the blood group.



"PHASE/VFK" by Jordan Eagles, 2008

60x72x3, Blood preserved on Plexiglas, UV resin

Courtesy of the artist

Replacing lost blood with something new has been on the minds of the learned for centuries. With the acquired knowledge that blood is a fluid whose essence keeps a man going, in the past various whimsical transfusions were attempted with liquids – such as ale, wine, opium and even milk – which were regarded just as essential to life as blood. At the turn of the century Karl Landsteiner (1868-1943), an Austrian doctor with a keen interest in the processes involved in immunity, demonstrated that you cannot pour any old blood into a patient. The nature of blood is not always the same from person

to person. Landsteiner was the first to identify the four main blood groups defined by antigens on a red blood cells' surface – A, B, AB, O – and the first to establish that a patient's blood group must match the blood group which is being transfused. Or else the patient will die.

The surface of red blood cells is riddled with millions of antigens. However, there are three main ones which are also the cause of blood transfusion accidents: antigens A, B and O. A given individual has either A antigens, or B antigens, or both (AB) or neither (O) on the surface of his or her red blood cells. Individuals with blood group A, produce B antibodies. So if they receive B group blood, their immune system will react and destroy the transfused blood cells. The opposite holds for people with group B blood. Individuals who are AB are fortunate in that they can receive either A or B blood since they produce neither B nor A antibodies respectively. The less fortunate blood group is the O blood group since it is fairly rare and can only receive blood from the same blood group. However, since a person whose blood group is O produces neither A nor B antibodies it can be transfused to all patients, i.e. A, B, AB and O blood groups. Hence its name: universal blood group. The obvious question is then: how can we make limitless amounts of universal blood?

In order to make something, you have to know what its component parts are. What is it that defines blood group A for example? A is an antigen found on the surface of red blood cells. This particular antigen is determined by a carbohydrate structure on the end of oligosaccharide chains on

glycoproteins and glycolipids lodged in the cell's membrane. Blood group A is defined by a terminal α -1,3-linked N-acetylgalactosamine (GalNAc). Blood group B is defined by a terminal α -1,3-linked galactose (Gal). And blood group O (which should really be pronounced 'zero') lacks both of these monosaccharides but instead is defined by an α -1,2-linked fucose. If there was a way of wiping off the monosaccharide entities (GalNAc and Gal) on A cells and B cells respectively, then blood groups A and B could be converted into the universal blood group O. What scientists then needed to find was something very small which could snap off the monosaccharide tips: an enzyme of some sort.

In fact, two enzymes were needed: one which could cleave the GalNAc entity, and one which could cleave the Gal entity. It took the best part of 25 years for scientists to discover two bacterial glycosidases – α -N-acetylgalactosaminidase and α -1,3-galactosidase A – which have the power to cleave and discard the GalNAc and Gal entities thus converting a red blood cell into a cell with neither a recognisable A nor B blood group antigen. In other words, they can convert A and B blood groups into a universal O blood group. Alpha-N-acetylgalactosaminidase is known in greater molecular detail than its homolog α -1,3-galactosidase A. Surprisingly, unlike other glycosidases of the same family, it needs the help of a cofactor (NAD⁺), which is nestled in the depths of a narrow tunnel, to cleave the GalNAc monosaccharide. Another part of the enzyme forms a crater which is large enough to accommodate an antigen from which the monosaccharide tip can be cleaved.

The discovery of both glycosidases is of great importance and could save many many lives in the future. It is not the first system which has been

thought up but may be the one which conjures up the least problems. Transfusions of haemoglobin solution are possible but haemoglobin doesn't react the same way on its own as it does inside a cell, and the oxygen isn't released. Hiding surface antigens by using a product that acts like minute fans on the cell's surface, which actually whisks antibodies away has also been devised. Stem cell production of O type red cells is also a possibility but 'young' human stem cells are not available. Erythropoietin can also be injected into a patient to boost red cell production; this can be used for patients whose religion forbids blood transfusion for example. But it cannot make a large amount of blood in a small amount of time. And when a patient is in danger, he or she doesn't have the time to wait.

So vacuuming the A and B antigens off red blood cells does seem to be a very elegant way of converting any red blood cell to the universal blood group. However, problems may arise. Do the converted cells react the same way if their surface has been modified? Are the bacterial glycosidases specific to the A and B antigens or could they possibly cleave other molecules on the cell's surface? Besides, one 'A cell' has one million A antigens on its surface, which demands a very resourceful glycosidase! And ridding red cells of their big A and B antigens will not rid them of the smaller antigens which also coat a cell's surface. As a consequence, if someone is in need of regular transfusions – as is the case for a number of diseases – he or she will gradually create an immune response to the smaller antigens. The problem is a tricky one to solve. Landsteiner established the different blood groups in the beginning of the 20th century, and a century later it seems that we are getting closer to finding a way of creating the red juice that keeps us alive.

Cross-references to Swiss-Prot

Alpha-N-acetylgalactosaminidase, *Flavobacterium meningosepticum*: A4Q8F7
Alpha-1,3-galactosidase A, *Streptomyces griseoplanus*: B1V8K7

References

1. Liu Q.P., Sulzenbacher G., Yuan H., Bennett E.P., Pietz G., Saunders K., Spence J., Nudelman E., Levery S.B., White T., Neveu J.M., Lane W.S., Bourne Y., Olsson M.L., Henrissat B., Clausen H.
Bacterial glycosidases for the production of universal red blood cells
Nature Biotechnology 25:454-464(2007)
PMID: 17401360
2. Boyce N.
Out for blood – Cooking up an alternative to the red stuff is proving a tough task
New Scientist Magazine, issue 2110, November 29th 1997