proteinspotlight
> ONE MONTH, ONE PROTEIN <

Issue 220, December 2019

www.proteinspotlight.org

dropping barriers

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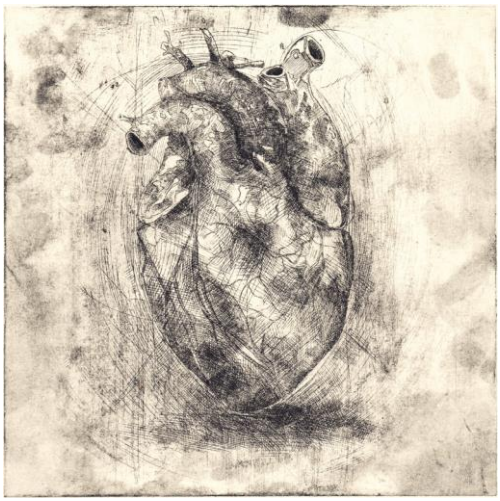
Blood. It is deep red, liquid and essential to life, and courses through us from the very early stages of our development to our final gasp. It cannot have taken long for our ancestors to make the link between blood and life. They will have seen the rich red fluid seep from wounds alongside the lifeless bodies of animals they had just hunted down, and understood that the same fluid flows through their own bodies. Blood is indeed a tissue (albeit liquid) of vital importance, composed of myriads of crucial cells and nutrients, which is why – when lost – it is transfused. There is a snag however: no two bloods are identical. But all human bloods can be sorted into well-defined groups of which the most representative are the A, B, AB and O blood groups. The O blood group can be transfused to everyone, while the other blood groups cannot. This is why scientists have been searching for ways, literally, to shift A, B and AB blood types to the 'universal' O blood type – which could resolve the problem of insufficient stocks in blood banks. There have been several attempts, none of which conclusive. One more promising attempt involves bacteria from our gut microbiome, and two enzymes: a D-galactosamine deacetylase and a D-galactosamine galactosaminidase.



'Beats', etching by Rosie McLay, Bristol, UK

Courtesy of the artist

It may be common knowledge today but it was only during the 17th century that the English physician William Harvey suggested that our blood goes round in circles inside us. With the discretion of a true gentleman he wrote: "I began privately to think that [blood] might rather have a certain movement, as it were, in a circle…" Until then, physicians had believed that our lungs were responsible for propelling our blood through our body. Blood itself was the result of food we ate, and was then soaked up by our tissues on a daily basis. But when Harvey considered the amount of blood that actually flows through the human body and studied more closely the anatomy of a heart, he concluded that the heart's role is to beat and pump blood around our body in a circle.

It was also in the 17th century that physicians attempted to make the first blood transfusions. More often than not however, they would be lethal although no one could explain why. By the 19th century, scientists had understood that mixing bloods usually caused them to agglutinate, and thought that this might be due to bacterial infection. The Austrian immunologist Karl Landsteiner finally paved the way to a deeper understanding when he mixed the red cells and plasma from the blood of six healthy colleagues. On this basis, he was able to determine three human blood types: A, B and C (which was to become the universal 'O'). The red cells carried what he termed the 'agglutinogens' (or antigens) A or B, or carried none at all (O), while the sera carried the 'agglutinins' anti-B or anti-A, or indeed both (O), respectively. Barely a year later, in 1902, a fourth less frequent blood group emerged: AB, where red cells carry both antigen A and antigen B while the plasma carries neither anti-A nor anti-B.

Many other blood types have been unveiled since – among which the widespread Rhesus (Rh) blood type – but Landsteiner determined the most relevant. At the turn of the 20th century, the knowledge acquired on blood types was almost purely

mathematical, and it was only towards the 1940s that the molecular nature of antigens and antibodies was beginning to be divulged. Today we known that antigens A and B are highly glycosylated mucin-type glycoproteins defined by the combination, presence or absence of four different types of monosaccharides responsible for the antigens' specificity: acetyl-galactosamine, N acetyl-glucosamine, fucose and galactose. In a nutshell, antigens A carry a terminal N acetyl-galactosamine monosaccharide and antigens B carry a terminal galactose.

Blood type O is invaluable in that it can be transfused to everyone. What is more and though it remains to be proved, blood groups A and B may well have been built upon a founding 'O' antigen present on red blood cells: pop N acetyl-galactosamine onto it and you have an A antigen, or replace it by a galactose and you have a B antigen. Conversely, if scientists could just whip the terminal monosaccharide off antigens A or B then, in principle, they could create blood type O. Since the 1980s, researchers have actually used enzymes to do just this. Though their efforts did meet with a certain success, the quantity of enzyme needed was too demanding, or the residual antigens left on the red cells caused blood agglutination nevertheless. Likewise, researchers have also had a go at generating O type red blood cells via stem cell technologies, but the process remains too costly.

Recently, scientists discovered two bacterial (*Flavonifractor plautii*) enzymes from our gut microbiome that work in unison to section off the N acetyl-galactosamine of the A antigen on red blood cells, thus shifting the blood type from A to O. It is a two-step process where a galactosamine deacetylase (GalNAc deacetylase) begins by deacetylating galactosamine on A antigens only. This deacetylated product then becomes the substrate for D-galactosamine galactosaminidase (GalNase) that performs the second and final step of the process by cleaving galactosamine clean off the antigen. What makes GalNac deacetylase and GalNase more trustworthy than the other systems that have been used up to now? They are specific: no compound other than A antigens are deacetylated and, as a consequence, only the galactosamines of A antigens are cleaved.

The combination of GalNac deacetylase and GalNase to convert A blood type to O seems promising although the possibility of residual A antigens still needs to be looked into. This all sounds very anthropocentric. Certainly, we need to know the molecular intimacy of antigens A and B for successful blood transfusions and possibly, also, for organ transplants. *F.plautii*, too, will not have produced two enzymes for the sake of human comfort, and neither are the A and B antigens present on red blood cells purely to define human blood groups. What is more, A and B antigens are found on many other tissues and, as glycoproteins, have all sorts of functions: structural, protective and regulatory, or they can be an integral part of molecular transport, protein folding and development, or even act as hormones, enzymes and recognition sites. An intriguing development: enzymes such as GalNac deacetylase and GalNase may provide an explanation for what is known as the 'acquired' B phenomenon where the blood type of patients has inexplicably shifted from A to B. It may also explain why forensic samples of intact red blood cells taken from two different body parts of a woman's body, that had been sectioned and thrown into the River Thames teeming with bacteria, revealed two different blood groups.

Cross-references to UniProt

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A type blood alpha-D-galactosamine galactosaminidase, *Flavonifractor plautii*: P0DTR5

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Protein Spotlight (ISSN 1424-4721), http://www.proteinspotlight.org, is published by the Swiss-Prot group at the Swiss Institute of Bioinformatics (SIB).