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The Christmas factor

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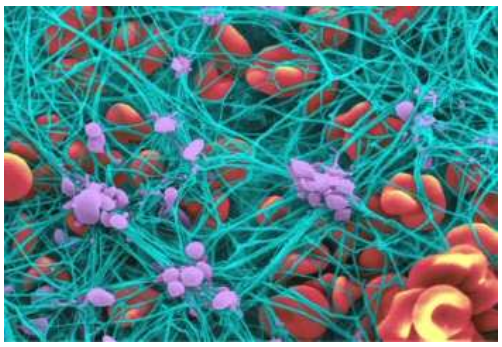
This is not an article about what multiplies your cholesterol level over the Christmas period. Or about what brings on – for some – terrible bouts of depression as the festivities draw in on them. But it does have to do with December 25th…in a way. The 'Christmas factor' is a protein whose deficiency was first discovered in the 1950s in a little boy by the name of Stephen Christmas. Also known as factor IX, or FIX, it is involved in blood clotting and its deficiency causes the rare form of congenital male hemophilia: hemophilia B. And coincidences being what they are, the article announcing the discovery of the Christmas factor was actually published in the 1952 Christmas edition of the British Medical Journal!

The art of coagulation is not recent. Primitive forms of the cascade probably existed in jawed vertebrates 450 million years ago. The first recordings of troubles in blood clotting are found in Jewish texts in 200 A.D. The reference is indirect and suggests the exemption of circumcision of any male subject if two of his brothers had already died of bleeding as a consequence of the ritual. The first modern description of haemophilia was made by John Conrad Otto – an American physician – in the very beginning of the 19th century, where he described the predisposition of the male members in certain families to suffer from frequent haemorrhages.

The case of haemophilia running through the British Royal family – namely Queen Victoria and her descendants – is now famous. Many of us have had to puzzle out the genetics behind the disease – sometimes referred to as the Royal disease – which appeared as a result of a spontaneous mutation in Queen Victoria's eighth child and son: Leopold. Leopold died young from a brain haemorrhage but left behind him two daughters who, unknowingly, were at the heart of the spread of haemophilia, which struck many royal families throughout Europe and Russia. The disease died out completely due to the lack of effective treatment but also war. As a consequence, it is not known today whether Queen Victoria's son suffered from haemophilia B, or the more classic form of haemophilia: haemophilia A.

Both forms of haemophilia are X-linked recessive congenital diseases, but their mutations are different. Haemophilia B is caused by a mutation which results in the deficiency of the Christmas factor (FIX) and, as a result, is also known as the Christmas disease. It is the rare form of haemophilia and affects 20% of the patients.



A blood clot

Courtesy of Yuri Veklich and John W. Weisel
University of Pennsylvania School of Medicine

In the beginning of the 20th century, the disease was just known as haemophilia, a blood clotting disorder. However, towards the middle of the century, an important observation was made. The blood of one haemophiliac patient could clot the blood of another. This meant that there were two forms – at least – of haemophilia, and they were named haemophilia A and haemophilia B. Haemophilia B was first described in Stephen Christmas.

As the 20th century rolled on, it became evident that the process of blood coagulation was far more complicated than had been initially thought. Today, at least twenty different proteins are known to be directly involved in blood coagulation or coagulation inhibition. The British biochemist R.G. MacFarlane was one of the first to describe the blood-clotting cascade as we know it today. And the Christmas factor is at the heart of it.

If a blood vessel's endothelium is damaged, or activated by various chemicals, cytokines or inflammation, it presents what is known as the Tissue Factor (TF) to the blood stream. Tissue factors are found on the surface of platelets, which synthesize a number of proteins involved in blood coagulation. With the help of another factor, FVII, TF activates FIX – the Christmas Factor. FIX then activates FVIII which in turn activates FX, itself directly involved in thrombin generation and ultimately fibrin formation. Haemophilia A – the most common form of haemophilia – is a deficiency of FX. FX continues to nourish the blood clot process by activating FIX in a kind of feedback loop, in which a further factor – FXI – activates FIX which, with FVIII, activates FX. The net result is that FIX activates FX via two pathways.

How? FIX is made up of four different domains: a gamma-carboxyglutamic acid (Gla) domain, two epidermal growth factor domains (EGFI and II) and a serine protease domain. FIX binds to the platelet surface with the TF/VII complex via its Gla N-terminus region. In its activated form, a short peptide is cleaved between EGFII and the serine protease. This results in a light chain (Gla, EGFI and II) and a heavy chain (the serine protease), which are held together via a single disulfide bond. FVIII is thought to bind to the EGFII and serine protease domain of FIX. There are a number of calcium and magnesium binding sites in the light chain of FIX. Both of these ions may confer a tertiary structure to the Gla domain which in turn would twist the EGFII and serine protease domain in such a way that FVIII can bind to them. FIX could then act as a serine protease and activate FVIII which, in turn, would activate FX…

Though the process may sound as entwined as the tinsel we put on our Christmas trees, the point is that FIX – i.e the Christmas factor – is essential in the blood clotting process and its deficiency causes severe problems. Treatment against haemophilia was poor until scientists achieved a greater understanding of blood groups and coagulation – which was only in the middle of the 20th century. Today patients can benefit from plasma-derived factors or recombinant factors, and gene transfer therapy may well be the future treatment for haemophilia. One of the greatest problems resides in haemophiliacs who develop inhibitors to the treatments, so drugs which could bypass the FIX/FVIII pathway are also needed. Inversely, thrombosis could be treated by designing drugs which would interfere with the interactions between FIX and TF, or FIX and FVIII, thus preventing coagulation.

Stephen Christmas spent a lifetime fighting for treatments for haemophiliacs and lived up to his name in many ways. When the article announcing the discovery of the Christmas factor was published in the 1952 Christmas edition of the British Medical Journal, it met with some negative reactions. Should a disease of any sort be related to the image of Christmas? The authors answered somewhat sarcastically that the precursor protein of the Christmas factor would not be called the 'Christmas Eve factor'… Sadly, Stephen Christmas died at the age of only 46, from HIV contracted through treatment with tainted blood products… just five days before Christmas 1993.

Cross-references to Swiss-Prot

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