Pentraxin 3 – A new player in twinning frequency

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Grace has had a passion for research since high school, when she was given the opportunity to work with a research team at a major Brisbane hospital. She has a particular research interest in the gene interplay involved in adipocyte differentiation and its implications on obesity.
Grace hopes to fulfil the bench-to-bedside philosophy during her career, where she can use her passion for scientific research to improve patient treatment.

The conception of dizygotic twins is a complex trait.

It is thought to be influenced by a variety of environmental and genetic factors and displays significant regional variation in prevalence worldwide. [1] For example, in Sub-Saharan areas of Africa, twinning is very common (~23 per 1000 pregnancies), while in Asia twinning is much rarer (~5-6 per 1000 pregnancies). [2] Recent research has sought to determine the reasons behind the increased frequency of twinning in regions of Sub-Saharan Africa. Independent studies of women from Gambia and Upper East Ghana have given insight into gene mutations which may possibly increase the fertility of women and hence the frequency of twinning. Specifically, it was found that certain single-nucleotide polymorphisms (SNPs) in the gene of pentraxin 3 (PTX3), a key player in human fertility and innate immunity, occurred in higher frequency amongst the mothers of twins. [3] This report will review the known functions of PTX3 in immunity and fertility and their relation to twinning frequency.

Pentraxin 3 in innate immunity

PTX3 is a soluble pattern recognition receptor, which belongs to the acute phase reactants superfamily. [4] In the innate immune response, PTX3 is produced in response to primary pro-inflammatory signals such as interleukin 6 (IL-6) release or toll-like receptor activation. [5] It participates in immunity by recognising pathogens, facilitating complement activation and opsonisation. [6] Indeed, it is involved in immune defence against *Aspergillus, Pseudomonas, Salmonella, Mycobacterium tuberculosis*, cytomegalovirus and influenza. [7-9] Known mechanisms of anti-pathogenic action include the binding of sialylated ligands on PTX3 to membrane proteins such as haemagglutinins found in influenza viruses and cytomegaloviruses. As haemagglutinins are used by viruses for fusion and entry to host cells, the binding of PTX3 ligands to the haemagglutinins can block this function and hence lower the chance of viral infection. [7,8] The anti-viral actions of PTX3 against cytomegalovirus can also activate downstream immune components such as interferon regulatory factor 3 (IRF3) and the interleukin-12/interferon gamma (IL-12/IFN)-γ-dependent effector pathway, which in turn heighten anti-fungal defences against species such as *Aspergillus*. [8] Previous experiments performed by Garlanda et al. also show that PTX3-null mouse models were more susceptible to fungal infections, suggesting that PTX3 plays a non-redundant antifungal role. [10]

Pentraxin 3 in fertility

PTX3 is not only a major player in immunity, it has also been demonstrated to be linked to fertility in various studies. Specifically, PTX3 interacts with proteins such as TNF-stimulated gene 6 (TSG6) and inter-alpha-trypsin inhibitor (IαI) to form multimolecular constructs which facilitate cross-linking in the hyaluronan matrix that surrounds the cells of the cumulus oophorus. [11] This is crucial to the stability and organisation of the cumulus matrix, as shown in animal studies where PTX3-null mice produced ova with abnormal cumulus oophorus, which led to lower litter counts. [12,13] The infertility resulting from PTX3 knockout is not surprising as a functional cumulus oophorus is required for oocyte maturation, movement to oviduct and penetration by sperm. [14-16] Notably, mouse and human PTX3 are highly conserved, suggesting that PTX3 may play a similar role in humans. [4] Further supporting the key, non-redundant roles of PTX3 in fertility is the finding that PTX3 is one of the most highly upregulated genes during the pro-inflammatory cascade at the foetal-maternal interface, which is crucial to decidualisation, blastocyst invasion, anchorage and implantation. [17-20]

Pentraxin 3 in twinning

It is clear that PTX3 plays a crucial role in immunity and fertility. Tying all these findings together is research by Sirugo et al. and May et al. which demonstrate associations between twinning, female fertility and PTX3 SNPs in humans. [3,21] Sirugo et al. demonstrated that the frequency of certain PTX3 haplotypes differed in frequency between mothers of twins and mothers without twins in a sample of 130 Gambian sister pairs ($p = 0.006–3.03x10^{-6}$, depending on haplotype). [3] In concordance with this, data from May et al. based on a population study suggest that those findings may indeed be due to increased fertility conferred by the PTX3 mutations. [21] It was found that women with more than12 children had SNPs in PTX3 causing the highest production of PTX3 and that women with less than 2 children had SNPs which conferred the lowest production of PTX3. Specifically, rs6788044 SNP, which was associated with the highest PTX3 production ($p = 0.003$), was also associated with the highest fertility ($p = 0.043$). In addition, increased *ex vivo* LPS-induced PTX3 production, suggesting better immunity, was also associated with increased fertility ($p = 0.040$). [21]

Could complex gene interplay be the reason for higher rates of twinning in Sub-Saharan Africa?

Conclusion

Taken together, the data suggests that PTX3 may contribute to the high rates of twinning in Sub-Saharan Africa. As increased PTX3 expression confers improved innate immune response, local selective pressures due to disease may skew epigenetic controls to favour these particular variants in particular populations where a strong immune response is crucial. [3] Certain SNPs of PTX3 which are selected for also confer increased fertility, via mechanisms such as increased cumulus oophorus stability and regulation of the pro-inflammatory cascade of implantation. While the role of PTX3 in multiple ovulations - a primary factor of dizygotic twinning - is still unclear, the contribution of PTX3 to successful implantation is also vital to twinning, by increasing the chance of survival of multiple blastocysts. In conclusion, the available evidence suggests that PTX3 may be an important contributor to twinning, at least in some African populations.

Conflict of interest

None declared.

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