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> ONE MONTH, ONE PROTEIN <

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nausea

Vivienne Baillie Gerritsen

Food poisoning is an ordeal. The body empties itself, with no respite, until nothing is left – neither vitality in you nor food in your system. It is less a single food item you have ingested which causes the unpleasant experience than the poison that was lurking in the smoked salmon, or the oyster, or the steak tartare you helped yourself to. Though we tend to curse our system when it happens, we should in fact be encouraging it. Why? Because it has sensed an ingested toxin that could be harmful to us. The fastest and most effective way of dealing with the toxin is to rid us of everything we have eaten. It so happens that a similar phenomenon occurs in the majority of pregnant women. During the first months of pregnancy, nausea hits many women the moment they rise in the morning or smell certain foods, or drink, during the course of the day. Though disagreeable to say the least, it is thought to be both for the mother's and the developing child's good. Indeed, morning sickness, as it is commonly known, could be linked to the potential ingestion of detrimental toxins, and to the presence of a protein known as GDF15.

Carl-Albert Angst (1875-1965)

courtesy of the artist's family

Morning sickness, also known as 'nausea and vomiting of pregnancy' (NVP), usually lasts for the first three months of pregnancy. More precisely: from the fourth to the sixteenth week, though it may stretch further. It so happens that during this time the foetus is at its most vulnerable while developing two of its most important organs: the heart and the brain. The mother, too, is less protected as her immune system has been weakened to ensure that her child – much like an organ transplant – is not rejected. The majority of pregnant women, as many as 70%, suffer from NVP. So, surely, there must be a reason for it. Does it, for that matter, not also exist in other mammals? In the 1990s, scientists suggested that NVP probably occurs to protect the mother and the child from toxins that could be damaging. In a way, it is Mother Nature's way of ensuring her legacy. Either toxins have actually been ingested, or the feeling of nausea keeps the mother away from items susceptible to contain any. If this is indeed the origin of NVP, though perhaps not elegant, the result is certainly simple and effective.

In the recent past, scientists discovered a protein whose level in the blood of pregnant mothers can increase hugely – sometimes dramatically. More intriguing, perhaps, is the find that the protein is mainly – but not exclusively – of foetal origin. Known as growth differentiation factor 15, or GDF15, the protein is normally present in many tissues in humans – male or female. It seems to be expressed when our bodies are subject to a form of stress and is thought to have a protective role of some kind, to such an extent that is has been dubbed the 'survival protein', though its exact role has yet to be unveiled. In fact, over the years, the protein's involvement in such a diverse array of biological functions has had it baptised MIC-1, NAG-1, PTGFB, PDF, PLAB... However, in the light of protection against toxins, GDF15 and pregnancy make utter sense. The foetus seems to pump GDF15 into its mother's blood to ensure its own protection while ensuring the mother's too – in a sort of win-win situation.

GDF15 is a protein hormone. It belongs to the transforming growth factor beta (TGFβ) superfamily that plays vital roles in embryonic development, cellular homeostasis, cellular growth, cellular adhesion, cellular migration, cellular proliferation and apoptosis – although GDF15, itself, diverges from the other members of the superfamily by the number of cysteine residues in its sequence. The N-terminus of the protein is long (about 200 amino acids) and necessary for the correct folding of the active hormone (about 100 amino acids long), which is active once dimerized. GDF15 may exist in three different forms in the cell, i.e. as 1) a pro-GDF15 monomer, 2) a pro-GDF15 dimer, and 3) the mature active homodimer which is subsequently secreted. The inactive pro-GDF15 monomer is thus roughly 300 amino acids long. Its C-terminal contains cysteine residues which link to a second pro-GDF15 monomer to create the inactive pro-GDF15 dimer. It seems that both the inactive pro-GDF15 dimer and the active form are secreted. However, pro-GDF15 dimer binds to the extracellular matrix where it is stored while the active GDF15 dimer is released into the circulation.

Back to morning sickness. Although GDF15 is naturally present in humans, we now know that its occurrence increases in most pregnant women and is mainly of foetal origin. In fact, the severity of NVP seems to be linked to how sensitive the mother is to the protein hormone GDF15. This sensitivity depends on the amount of GDF15 naturally present in mothers when non-pregnant. In short, if women have relatively high levels of GDF15 in their blood when they are not expecting a child then they will probably suffer from NVP which, from a purely biological point of view, is a good thing. It so happens that a more severe form of NVP exists – coined hyperemesis gravidarum, or HG. Women who suffer from HG (about 2% of pregnancies) are unable to eat or drink normally and end up losing weight, which can complicate pregnancy. However, although HG can prove to be violent and some women have to be hospitalized, the foetus suffers no harm. It is believed that HG is probably caused by the presence of a specific isoform of GDF15. On the other hand, women who have relatively high levels of GDF15 in their blood when non-pregnant seem to be less at risk of developing HG.

As a protein hormone, GDF15 binds to receptors to trigger off downstream signalling pathways in cells. What pathways does GDF15 promote? How does it work? Does it bind to more than one receptor? Present in many tissues, its role is still poorly defined but it has been found to be involved in many different instances: obesity, diabetes, cardiometabolic disease, ageing, neurodegenerative disease, NVP, appetite, cancer… Consequently, GDF15 is expected to bind to a variety of receptors. What we know for sure today, however, is that GDF15 binds to a receptor known as GDNF family receptor α-like protein, or GFRAL, which is only expressed in the hindbrain. In fact, GDF15 binds to a heterodimer of GFRAL and a protein kinase receptor known as RET, and it is this bond that is ultimately responsible for morning sickness, or what scientists call 'aversive responses'.

One question arises: why do most women feel much better after the first trimester of pregnancy? This is now quantitively explained by a net drop in the presence of GDF15 in their blood. But what about safety? Naturally, the embryo – now a foetus – is less vulnerable but not completely out of harm's way. However, the foetus now needs all the energy it can get to continue its development, and this fact may well outweigh that of producing GDF15 and the risk of possible poisoning or infections. The fluctuating rate of GDF15 in a mother's blood and her susceptibility to NVP or HG is intriguing. Perhaps mothers who are diagnosed as prone to HG – or to violent bouts of NVP – could be sensitized to GDF15 before becoming pregnant. This would avoid taking drugs which may lessen the symptoms but could probe to be harmful to the child. We only have to think of the antiemetic thalidomide tragedy (*see protein spotlight issue 117*) in the late 1950s and early 1960s which caused thousands of miscarriages in many countries, and as many children born with deformities that were more or less severe – and continue to be so today.

Cross-references to UniProt

Growth/differentiation factor 15, *Homo sapiens* (Human): Q99988

References

1. Fejzo M., Rocha N., Cimino I., et al.
   GDF15 linked to maternal risk of nausea and vomiting during pregnancy
   Nature 625: (2024)
   PMID: 38092039

2. Assadi A., Zahabi A., Hart R.A.
   GDF15, an update of the physiological and pathological roles it plays: a review
   European Journal of Physiology 472:1535-1546(2020)
   PMID: 32936319

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