

## life's first breath

Vivienne Baillie Gerritsen

We give very little thought to the first breath we took as we entered this side of reality, and yet it was one of the most traumatic experiences we have ever been through. So much so, it is probably not such a bad thing that we have no – conscious – recollection of it. Each one of us spent the most part of nine months floating in amniotic fluid inside our mother, with oxygen being pumped into us via the umbilical cord. Once born, the umbilical cord is taken away from us and we have to find another way of providing our body with oxygen. Fast. That's when the tiny newborn – that we all were – starts using its airways which, up to that point, had been on standby. Something, however, has to boost them into action. Recently, researchers discovered the doings of a protein, known as 'teashirt homolog 3', which has shown that it most probably has a direct role in life's first breath - not in sparking it off but in preparing the grounds to welcome oxygen and deliver it to every part of our body.



Life's first breath, by Maria Pace-Wynters

Courtesy of the artist

Why do we breathe in the first place? The question really is: why do we need oxygen? Oxygen is used in the process which makes energy out of the food we eat. Without it, we would not be able to synthesize ATP and our body would therefore be deprived of the vital molecule which drives all the biosynthetic pathways and physiological processes we need to keep us alive. In order to capture the oxygen, Mother Nature provided us with airways – such as lungs and a nose – to breathe it in, and blood

to distribute it to every nook and cranny of our body. Likewise, the same airways and blood system get rid of carbonic dioxide which is the waste product that arises from the use of oxygen. Consequently, the process of breathing in, and breathing out, is paramount to say the least, and perhaps best illustrated by the notion that life is determined by both our first breath and our last.

The act of breathing is a complex one. It is not just a matter of letting the surrounding oxygen leak into our nose or mouth, from where it will drift into the blood system. Two airways – the upper one and the lower one – have to be set into motion. In a nutshell, the upper airways are the system we use above our shoulders to provide an air flow, such as our nose and the windpipe; the lower airways are situated below the neck, such as our lungs. When a newborn finally emerges from its mother's womb, a whole set of muscles, airway openings, motoneurons and hordes of biochemical pathways are triggered off so that the first breath of air can enter the mouth and be pushed down to the lungs which will have just started their rhythmic movement for a lifetime of inhalation and exhalation.

Teashirt 3 is not a newly discovered protein. It belongs to the large family of zinc finger proteins which are transcriptional regulators, so named because they use zinc ions to stabilise internal structural folds that are capable of

binding typically to DNA or RNA. Teashirt 3, in particular, is involved in the regulation of developmental processes within the upper and the lower respiratory system, as well as in the differentiation of uretic smooth muscle for instance. It is also known to be involved in the development of Alzheimer's disease together with caspase 4. All in all though, the most surprising role teashirt 3 has is, without a doubt, its connection with a newborn's very first breath.

Indeed, very recently, researchers demonstrated that when teashirt 3 was deficient in mice, the rodents were incapable of taking their first breath and, as a result, died almost instantly. The reason for this is twofold. Seemingly, teashirt 3 has a direct role both in the opening and the shutting of upper airways, and the rhythmic heave of the lungs as they inhale and exhale. Under such circumstances, it is not difficult to grasp the notion that deprived of one of these events – or indeed both – a newborn has little chance of surviving.

In detail, with regards to the upper airways, teashirt 3 seems to be involved in controlled cell death of cranial motoneurons. To be sure, when teashirt 3 is deficient, motoneuron apoptosis is abnormally increased thereby tampering with the neuromuscular control for the flow of

oxygen in the upper airways. How exactly this happens is still unknown but teashirt 3 may be important for the cell to cell signalling essential for the survival of embryonic motoneurons. It could be that teashirt 3 actually protects neurons from apoptosis. In the lower airways, teashirt 3 seems to be directly linked to the well-being of the chest pump. Without it, the respiratory rhythm generator (RRG), which governs the rhythmic contractions of the chest pump muscles, is disturbed. How is still unclear but it could have something to do with pH levels. When the umbilical cord is cut, unless there is a system to preserve the pH homeostasis, the RRG is not prompted. Hence the newborn is unable to breath.

This said, teashirt 3 cannot solely account for a newborn failing to draw its first breath. No protein acts on its own. However, teashirt 3 is certainly a key protein in the “simple” act of living. It is at the origin of our first breath and hence at the heart of our survival outside our mother's womb. And it must surely have a decisive role in our very last breath too. Besides this knowledge, getting to know teashirt 3 more intimately may well help to prevent neonatal deaths, which remain for the great majority unexplained. And who knows? Perhaps, one day, teashirt 3 will help to prolong life by lending us that extra puff.

---

## Cross-references to UniProt

Teashirt homolog 3, *Mus musculus* (Mouse) : Q8CGV9

Teashirt homolog 3, *Homo sapiens* (Human) : Q63HK5

Teashirt homolog 3, *Rattus norvegicus* (Rat) : D3ZKB9

## References

1. Caubit X., Thoby-Brisson M., Voituren N., Filippi P., Bévengut M., Faralli H., Zanella S., Fortin G., Hilaire G., Fasano L.  
Teashirt 3 regulates development of neurons involved in both respiratory rhythm and airflow control  
Journal of Neuroscience 30:9465-9476(2010)  
PMID: 20631175
2. Caubit X., Lye C.M., Martin E., Coré N., Long D.A., Vola C., Jenkins D., Garratt A.N., Skaer H., Woolf A.S., Fasano L.  
Teashirt 3 is necessary for ureteral smooth muscle differentiation downstream of SHH and BMP4  
Development 135:3301-3310(2008)  
PMID: 18776146