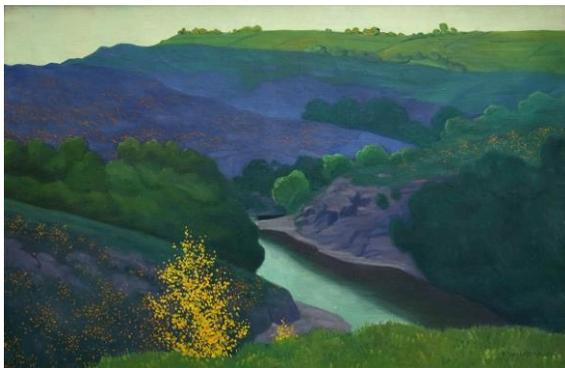


## in the beginning

Vivienne Baillie Gerritsen

It is one of the many mysteries of our existence. How does life begin? What gives the first nudge? Is there, for that matter, a primordial poke? Over the millennia, scholars have tried to define the actual notion of life as a whole – which may seem obvious to some, but just sit down for a while and give it a thought. How are creatures made? How do they begin? What, for instance, goes on inside a womb? Theories varied according to the knowledge of the times, and explanations shifted from the near mystical to the anatomical, closely followed by the cellular until the 1980s, when – thanks to the rise of novel technologies – researchers could consider embryology at the level of the molecular. Though we are still really asking the same questions, what we know about the making of life has been dramatically fine-tuned and we now delve into the minute, wondering which molecules drive cells to become one part of an organism or another. What factors kickstart the process of a cell's fate? Today, we have part of the answer: the tetra-peptide repeat homeobox proteins. Transcription factors without which the very first embryonic cell divisions would not occur.



Paysage de la Creuse (1925)

Félix Vallotton

Recordings of an interest in human development date back to Ancient Egypt. By the 18<sup>th</sup> century – and many dissections and theories later – two opposing schools had been established: the preformationists and the epigenesists. The preformationists believed that embryos were miniature completed organisms that floated in the maternal egg or in the sperm. They were the creation of God and, when their time came, they simply unfolded to grow into their mature size. The epigenesists, on the other hand, believed that organisms developed progressively from an egg, itself newly produced from unorganised material. It would take microscopes, and the science of cell

biology followed by that of molecular biology to finally grasp the subtle intricacies of embryogenesis we are aware of today. To cut a labyrinthine story short, upon fertilization by a sperm, the maternal egg becomes what is known as a zygote. A zygote is the very first cell each one of us emerged from to form a skeleton, a heart, a brain, a stomach, an immune system, feelings, thoughts, memories, creativity, language, eyes, a nose, a mouth, two legs, ten fingers and ten toes. The epigenesists were on the right track.

Zygotes are totipotent cells. That is to say that they have the power to build a whole organism, with all its different tissues and all their different kinds of cells. This ‘potency’ cannot only be explained by the DNA held within the zygote’s nucleus, i.e. its genome, because the great majority of the cells in our body carry the exact same genome in their nucleus. Yet, try as you wish, they are unable to create another you. So there must be something else going on. Cells are selected to become muscle cells or brain cells. They are driven to a certain fate. This is the essence of embryology. What drives this are molecular factors that regulate the transcription of genes and their translation into proteins – gradually urging a cell into one direction or another by switching sets of genes on or off. Little by little, division after division, cells will lose their potency, to become ‘soldier’ cells that are part of only one type of tissue: the brain, the blood, muscle and so on.

In fact, the totipotency of a zygote is lost very quickly. By the time the embryo is only composed of 4 cells, each cell is already beginning to head in a particular direction. By the eight-cell stage, taken independently, not one of the cells would be able to develop into a whole organism anymore. Once an organism is fully formed, most of its cells are only able to divide into a cell of the same nature: a muscle cell will give rise to another muscle cell for instance. Certain special cells, however, do preserve a certain potency, albeit diminished. These are known as stem cells. Blood-forming stem cells, for example, give rise to different types of blood cell. In brief, the fate of a cell can be seen as the expression, or not, of different sets of genes whose products may also go on to encourage the expression of others, or not.

One of the most stunning – yet invisible – cascades to occur must undoubtedly be the one that begins immediately after the formation of a zygote. First, though, the zygote needs to be given a small shove. Something has to ignite the flame and set things off. This moment has been called ‘zygote genome activation’, or ZGA. Literally, the zygote’s genome is stirred by transcription factors (TFs). The moment a zygote is formed, TFs leap into action to stimulate the expression of specific genes which, in turn, will stimulate the expression of others, thus kickstarting the development of an embryo and then the foetus. ZGA thus marks the very first transcription event in a new life.

Yes, but where do these factors come from, and what makes them burst into life – so to speak. As an illustration, let us consider three factors known as tetra-peptide repeat homeobox proteins: TPRXL,

TPRX1 and TPRX2. All three TPRXs are transcription factors which are highly expressed during the early stages of ZGA, each binding to specific regulatory DNA sequences on the promotor of genes directly involved in the event. TPRXL is the first to act as it is produced from dormant maternal transcripts already present in the egg. TPRX1 and TPRX2 appear shortly after, probably generated once the zygote is formed. Together, TPRXL, 1 and 2 ensure that ZGA actually occurs and that the early form of the embryo at the stage of a blastocyst is correctly formed, thereby ensuring correct implantation in the uterus. Though TPRX are far from the only TFs to be activated at this critical moment of embryo development, without them, ZGA does not happen.

In a way, TPRX factors are among those that mark the beginning of embryonic cell decline in potency. This may sound gloomy, but this critical tipping point is of great interest to researchers. Understanding ZGA in detail, getting to know – intimately – the factors that provoke it, grasping the notion of totipotency and pluripotency in molecular terms are studies that could help resolve some cases of infertility, as well as giving insight into the very early steps of embryogenesis and the possible onset of developmental disorders. What, too, if researchers were able to master human cells and use them to produce transplants – a heart for example. Science fiction? Not really. Remember Dolly? Studies of the like, however, are strongly discouraged on human embryos because of severe restrictions with respect to ethical considerations. And thankfully so, no doubt. It is about life, and its onset. Deeply entrancing, and yet disconcerting.

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## Cross-references to UniProt

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