150 years of Darwin's theory of intercellular flow of hereditary information

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In 1868, Charles Darwin published his Pangenesis theory, which proposed a mechanism for the flow of hereditary information between cells and generations. Pangenesis has since been disputed, but emerging evidence of cell-to-cell communication urges the reconsideration of this 150-year-old theory.

The theory of Pangenesis

In 1868, 9 years after the advent of *On the Origin of Species*, Charles Darwin published his two-volume book, *The Variation of Animals and Plants under Domestication*[1], in which he introduced the theory of Pangenesis. This was an attempt to strengthen the theory of evolution by providing a cellular or molecular mechanism of inheritance, and to understand the cause of variation upon which natural selection acts.

In the Pangenesis theory, Darwin proposed that in addition to cell division as a mean of transferring information, every cell also emits numerous particles or molecules called 'gemmules', which diffuse to and are 'united' with both somatic cells and germ cells. Moreover, Darwin proposed that gemmules could be transmitted from parents to offspring and could either function in the immediate progeny or remain dormant for generations and then be activated; the activation of gemmules would depend on the specific cells or other gemmules with which they were united. Importantly, Darwin proposed that the environment could modify gemmules, and thus that the composition of gemmules mirrors the organism's environmental exposure.

Pangenesis provided a potential explanation for a range of phenomena pertaining to inheritance and phenotypic variation, including 'prepotency' (analogous to Gregor Mendel's 'dominance', introduced in 1866), graft hybridization, reversion and the inheritance of acquired characteristics — a notion favoured by Jean-Baptiste Lamarck.

The fall

Following its publication, Pangenesis was severely criticized, mainly for two reasons. First, the proposed gemmules lacked evidence. Darwin envisioned that gemmules were "inconceivably minute and numerous as the stars in heaven", "barely visible under the highest powers of the microscope" and "contained within each bud, ovule, spermatozoon, and pollengrain". These speculations could not be validated at the time and were considered as "the fictions of the fancy" by the physician and microscopist Lionel Beale, and as "a pure invention" by the evolutionary biologist August Weismann. In a series of blood transfusion experiments, Francis Galton failed to detect fur colour changes in the offspring of silver-grey rabbits that were transfused with the blood of lop-eared rabbits; he concluded that the blood did not carry Darwin's hypothetical gemmules.

Second, Pangenesis attempted to explain a range of doubtful phenomena including the inheritance of acquired characteristics; but as the evolutionary biologist and geneticist Thomas Morgan commented, if this premise is not tenable, such a theory is unnecessary. Indeed, the historical dismissal of the inheritance of acquired traits greatly dampened the impact of Pangenesis, and conventional wisdom considers Darwin's belief in the inheritance of acquired characteristics a great mistake. The Pangenesis theory was quickly replaced by Weismann's Germ-Plasm theory, which postulated that information only flows from germ cells to somatic cells, and not vice versa (this is also known as the 'Weismann barrier').

Resurrection

If the history of science has taught us anything, it might be that absence of evidence is not evidence of absence. One hundred and fifty years after its original publication, the Pangenesis theory is reappearing in scientific literature following the emergence of new evidence. The hypothetical gemmules that carry hereditary information outside of cells are now being identified in modern forms. Cell biologists are intensely studying extracellular vesicles (such as exosomes) that are secreted from cells, which share the core features of gemmules. Exosomes can carry cell content such as RNA and proteins and thus transfer information between somatic cells, as in the

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case of cancer metastasis[2], or between somatic cells and germ cells[3]. Moreover, recent serum transfusion experiments in mammals have been shown to induce epigenetic signatures in sperm that enable transgenerational inheritance of paternal, liver-specific wound-healing responses. This suggests that soluble factors in the serum (of unknown identity, but possibly modern forms of gemmules) can indeed transfer acquired information from somatic cells to germ cells and thus induce the expression of parentally acquired traits in the offspring[3].

An increasing number of studies in plants, worms and flies now clearly support the notion that certain parental traits acquired through environmental experiences can be inherited[4]. There is also evidence in mammals to suggest that adaptations to diet, temperature, mental stress and chemical exposure can be transmitted to offspring, although the underlying molecular mechanisms are far less understood than in non-mammalian organisms[4]. In these cases, parentally acquired characteristics are possibly transmitted not through the DNA sequence but through epigenetic information carriers such as DNA methylation, histone modifications and RNAs in the germ line, or even outside the germ line, for example, through seminal fluid[3]. These emerging data weaken the Weismann barrier and lend support to Darwin's Pangenesis theory.

The principles and the unknown

At the heart of Pangenesis is the flow of (hereditary) information through gemmules, which enables environment–somatic, somatic–somatic and somatic–germ line interactions. This idea was visionary in Darwin's time and raised many outstanding questions that remain unresolved. For example, despite the identification of some physical forms of gemmules as exosomes or mobile RNAs, it remains unclear whether and how a specific life experience can be encoded by the labile epigenetic information carriers. In addition, if such 'coded' information is transferred from somatic cells to germ cells, by what mechanism are the data 'decoded' during development to precisely mirror in the offspring the parentally acquired traits? Especially in mammals, these changes must escape the extensive reprogramming processes that erase most epigenetic modifications first in the preimplantation embryo (to allow intergenerational inheritance) and then during germline development (to allow transgenerational inheritance)[4]. These quintessential questions represent our naiveté in understanding the nature of inheritance of acquired traits, particularly in mammals.

Interestingly, recent studies have suggested that RNA species found in mouse sperm and their associated RNA modifications can substantially augment sequence-encoded information by generating RNA secondary structures and functional diversity[5]. This newly appreciated complexity of RNA-based carriers of hereditary information may provide the information capacity needed to encode various acquired traits. Regulatory RNAs transferred from somatic cells to germ cells may carry information representing environmental exposure and introduce changes to the germ line that mirror the environmental input. Such modified RNAs may also provide means to bypass epigenetic reprogramming processes, as they are mobile and can act in *trans* to establish an epigenetic modification that could stably transmit an acquired phenotype. These speculations and preliminary data represent tantalizing directions for understanding the extent of epigenetic inheritance of acquired traits in mammals.

The ongoing scientific legacy

Darwin's Pangenesis should be credited also for the concept of cell–cell communication through extracellular molecular carriers, which resonates well with current exciting research into intercellular communication[2] and even extends to the population level, as exemplified by oral transfer of information in social insects, and to inter-species and cross-kingdom interactions, as exemplified by bidirectional exosomal transfer of small RNAs between plants and fungi in immune responses. These contemporary breakthroughs are expected to promote future studies on horizontal gene transfer, microbiome–host interactions, graft hybridization and plant–animal interactions.

Historically, the theory of Pangenesis has been neglected by the scientific community compared with Darwin's widely accepted theory of natural selection, which was presented in *On the Origin of Species* (1859). However, Pangenesis is of great value to Darwin's scientific system. In a letter to Joseph Hooker in 1868, Darwin wrote: "You will think me very self-sufficient, when I declare that I feel sure if Pangenesis is now stillborn it will, thank God, at some future time reappear, begotten by some other father, and christened by some other name." One hundred and fifty years later, Pangenesis is apparently reborn as a conceptual framework for the intercellular flow of hereditary information that continues to push the boundaries of science.

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