

Mesoderm

Mesoderm is one of the three germ layers, groups of cells that interact early during the embryonic life of animals and from which organs and tissues form. As organs form, a process called organogenesis, mesoderm interacts with endoderm and ectoderm to give rise to the digestive tract, the heart and skeletal muscles, red blood cells, and the tubules of the kidneys, as well as a type of connective tissue called mesenchyme. All animals that have only one plane of symmetry through the body, called bilateral symmetry, form three germ layers. Animals that have only two germ layers develop open digestive cavities. In contrast, the evolutionary development of the mesoderm allowed in animals the formation of internal organs such as stomachs and intestines (viscera).

Gastrulation is an early stage of development during which an embryo, then a single-layered ball of cells called a blastula, reorganizes itself into a three-layered ball of cells, called a gastrula. During this process, the primary germ layers, endoderm and ectoderm, interact to form the third, called mesoderm. Early in the reorganization process, a group of precursor cells that hold the potential to become either mesoderm or endoderm may form; this tissue is called mesendoderm. Mesendoderm has been found in species from Echinoderms, such as sea urchins, to mice, *Mus musculus*. The process that gives rise to the mesoderm also creates a dorso-ventral pattern within the mesoderm. This patterning of the mesoderm organizes cells in specific locations along the dorso-ventral axis, and a cell's location determines what kinds of cell it and its daughter cells can become (cell fate).

Mesoderm, along with the other two germ layers, was discovered in the early nineteenth century. In 1817 Christian Pander received an MD from the University of Würzburg, in Würzburg, Germany, after completing his dissertation. "Beiträge zur Entwicklungsgeschichte des Hühnchens im Eie" (Contributions to the Developmental History of the Chicken in the Egg) described how two layers of the chick embryo give rise to a third, outlining the process of gastrulation in the chick, *Gallus gallus*. Throughout his text, Pander wrote of both the independence and of the interdependence of these layers—while distinguishable, the layers appeared to work together to form organs.

Following Pander's discovery, a series of nineteenth century scientists investigated the formation and derivatives of the germ layers. Karl Ernst von Baer, professor of anatomy at the University of Königsberg, in Königsberg, Prussia, in his 1828 *Über die Entwicklungsgeschichte der Thiere. Beobachtung und Reflexion* (On the Developmental History of Animals. Observations and Reflections), extended Pander's concept of the germ layers to apply to all vertebrates. In 1849 natural historian Thomas Henry Huxley, in England, expanded the concept yet again, in his article "On the Anatomy and Affinities of the Family of the Medusae." Through his anatomical investigations of jellyfish, Huxley concluded that the two tissue layers he saw in the adult jellyfish bore the same relation to each other as the layers Pander had described in the chick embryo. When Huxley argued that the body architecture of the adult jellyfish was similar to those of vertebrate embryos, he united the vertebrate and invertebrate kingdoms and connected the study of growth and development, called ontogeny, with the study of relationships between organisms, called phylogeny. Huxley's observation that developmental stages reflected evolution set a trend, in that scientists began to investigate evolutionary questions by studying embryos. Those methods became foundational for the works of nineteenth century scientists like Charles Darwin, in England, and Ernst Haeckel, in Germany. Huxley employed the term mesoderm for the middle germ layer in the 1871 edition of his *A Manual of Anatomy of Vertebrated Animals*.

Toward the end of the nineteenth century, interest in germ layers erupted. As a result of the renewed association of embryology and phylogeny, some argued that universal relationships of the germ layers may exist throughout the animal kingdom. Germ Layer theory held that across all animal

species, each of the germ layers gives rise to a fixed set of organs that are homologous between taxa. Scientists like Aleksandr Kovalevsky at the University of St. Petersburg, in St. Petersburg, Russia, and Ernst Haeckel helped make the Germ Layer theory doctrinal for embryologists beginning in the late 1860s.

Some nineteenth century scientists, like Edmund Beecher Wilson, in the United States, and many scientists in Germany, including Wilhelm His, Rudolf Albert von Kölliker, and Oscar and Richard Hertwig, objected to the Germ Layer theory. These scientists often created their own theories of how the germ layers develop. For example, brothers Oscar and Richard Hertwig formed a concept called Coelom Theory, to explain the source and development of the mesoderm in phylogenetic terms. In their *Die Coelomtheorie. Versucheiner Erklärung des mittleren Keimblättes* (Coelom Theory: An Attempt to Explain the Middle Germ Layer) the Hertwig brothers contested homologous relationships between the germ layers across taxa. Instead, the Hertwigs saw the germ layers, especially the mesoderm, as raw materials that could develop into a variety of organs in response to different conditions of existence.

Germ Layer theory remained influential during the late nineteenth and early twentieth centuries. However, the doctrine was eventually dismantled in the early to mid twentieth century by scientists like Hans Spemann, at the University of Freiburg in Freiburg, Germany, and his doctoral student Hilde Proescholdt Mangold, as well as by Sven Hörstadius, working at Uppsala University, in Uppsala, Sweden. These researchers showed that the fates of the germ layers were not absolutely specified and that they varied across species. After such work, scientists increasingly experimented with embryos from different species, and they detailed how the mesoderm arises from the interactions of ectoderm and endoderm.

In 1969 Pieter D. Nieuwkoop, Director of the Hubrecht Laboratory in the Royal Netherlands Academy of Arts and Sciences, in Utrecht, Holland, published an article that addressed the question of how mesoderm develops in vertebrates. Nieuwkoop used the embryos of the salamander *Ambystoma mexicanum* to test the ability of different parts of the amphibian egg to differentiate into various types of cells. He separated the sections that would give rise to ectoderm and endoderm and allowed them to develop independently; he found that mesoderm could not form without the interaction of these two tissues. When Nieuwkoop recombined the ectodermal and endodermal regions, the endoderm induced mesoderm to form in the adjacent region of the ectoderm. Using those experiments, Nieuwkoop also demonstrated that the induction process establishes a polarity in the mesoderm, such that dorsal endoderm induces dorsal mesoderm, while ventral endoderm induces ventral mesoderm.

While Nieuwkoop was able to discern the roles of the germ layers for the induction of mesoderm, the signals involved in the genetic activation of the process remained unknown. Beginning in the mid-1980s, scientists started to determine the molecules responsible for mesodermal induction. They found that at least four families of protein-encoding pathways, or signaling factors, Vg1/Nodal, BMP, Wnt, and FGF, direct the induction and maintenance of mesoderm in vertebrates. In 2002 Eric Davidson and his colleagues at California Institute of Technology in Pasadena, California outlined the gene network that regulates specification of mesoderm and endoderm in the sea urchin, and Davidson further confirmed this network in 2012 with Sagar Damle.

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