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In "Selective Growth Stimulating Effects of Mouse Sarcoma on the Sensory and Sympathetic Nervous System of the Chick Embryo," Rita Levi-Montalcini [4] and Viktor Hamburger [5] explored the effects of two nerve growth stimulating tumors: mouse [6] sarcomas 180 and 37. This experiment led to the discovery that nerve growth factor [7] was a diffusible chemical and later to discoveries that the compound was a protein. Although this paper was an important step in the discovery of nerve growth factor [8], the term "nerve growth factor" was not used in this paper. It was instead referred to as a "growth promoting agent." The discovery of nerve growth factor [9] earned Levi-Montalcini and Stanley Cohen [10], who also discovered epidermal growth factor, the 1986 Nobel Prize in Physiology or Medicine [11].

This paper was published in 1951 in the Journal of Experimental Zoology [12], volume 116. During this time, Hamburger and Levi-Montalcini were studying the changes in neural development [13] based on various implantations of homogenous tissues, such as skin, muscle, or liver. They were trying to determine what was responsible for increases in nerve growth generated by limb implantations. Experiments by Elmer Bueker [14] showed that sarcoma 180 produced extensive nerve growth in sensory fibers. In this experiment, Levi-Montalcini studied these tumors to examine the specificity of sarcomas 180 and 37 to specific nerve types. She was able to differentiate between two types of nerve fibers, motor fibers and sensory nerve fibers.

In addition to sarcomas 180 and 37, carcinomas dbBR and C3HBA and implantations of mouse [15] placenta [16] were included in this experiment. All implanted tissues were obtained from Jackson Memorial Laboratory [17] in Bar Harbor, Maine, an important mouse [18] research laboratory, and were made from the mouse [19] to a developing chick [20] embryo. The two carcinomas were tumors of the mammary gland, and the mouse [21] placenta [22] was included to determine if the nerve growth was a response to mouse [23] tissue in general. The implantations were made slightly anterior to the hind limbs, and nerve growth was identified by silver staining, which was capable of differentiating between motor nerve fibers and sensory nerve fibers, an important aspect of this study.

The carcinomas dbBR and C3HBA produced inconclusive results since they were resorbed by the embryo. The tumors grew successfully on the chorio-allantoic membrane, a vascular membrane which surrounds the developing embryo. The chick [21] embryo resorbed the tumor tissue of the carcinomas, and these two were not discussed further. The sarcomas 180 and 37 grew vigorously in the chick [21] embryo. The growth of the two sarcomas proceeded in different ways. Sarcoma 180 formed compact masses which pushed adjacent tissues outward. Sarcoma 37 pushed through the nearby tissues with fibrous outgrowths. This sarcoma showed a tendency to extend toward and envelop the ganglia and other nerves tissues without entering those structures. Both sarcomas successfully increased nerve growth from adjacent ganglia. Both types of sarcoma were invaded by nerve fibers, indicating an attraction of sensory nerve fibers. This study also found that the sarcomas stimulated a specific type of sensory nerve, ventrolateral nerve fibers, while mediodorsal fibers did not react to the tumor. The sarcomas produced significant detours of the ventrolateral nerve fibers on the half of the embryo harboring the tumor. Initially the nerve fibers extended toward, and then detoured around, the sarcoma. The tumor growth then encompassed the surrounding nervous tissue, and large nerve bundles developed inside the tumor. The most striking difference in tissues affected by the sarcomas was the increased growth in the ganglia near the tumor. The spinal and sympathetic ganglia of the chick [21] showed not only an increase in volume, but also an increase in the number of nerve fibers extending from the ganglia. Furthermore, the growth is concentrated on the side facing the tumor.

The nerve growth stimulation was discovered to be a very specific signal. The signal was confined to ganglia and only to certain sensory neurons from the ganglia; the motor neurons showed no hyperplasia [24]. Studies of the spinal cord similarly showed no increase in nerve growth, providing further evidence that the nerve growth signal was specific to the ganglia and related nerve fibers.

This experiment showed that nerve growth factor [25] was a specific chemical signal, localized to certain nerve types and specific structures in the nervous system. The affected ganglia were significantly enlarged, in contrast to the spinal cord, another nervous tissue, which was not enlarged. The ventrolateral nerve fibers were found to invade the sarcomas in significant numbers, while a similar type of sympathetic nerve, mediodorsal fibers, did not respond at all. This paper was the first to identify a specific nerve growth signal, which led to the discovery of nerve growth factor [25] and a 1986 Nobel Prize.

Sources


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