The swing of architect genes

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Architect genes are responsible for organizing structures of the body during embryonic development. Some of them, namely the Hox genes, are involved in the formation of forelimbs. They are activated in two successive waves, enabling the formation of the arm, then the hand. A team led by Denis Duboule, a professor at UNIGE and EPFL, Switzerland, and Guillaume Andrey, from the Frontiers in Genetics National Research Center, uncovered the workings of this complex process.

A few days. This is the short period of time during which our body's construction plan is put in place, during its embryonic life. The appearance of limbs and vertebrae is orchestrated by a family of 'architect' genes called Hox, each providing precise instructions at a given time. Denis Duboule, a geneticist at the Faculty of Science of the University of Geneva (UNIGE) and at the Swiss Federal Institute of Technology in Lausanne (EPFL), demonstrated that these genes were aligned within our chromosomes according to the order of structures that will emerge: first the components of the shoulder, then the arm, and finally the fingers.

The cluster of Hoxd genes coordinates the operations of limb formation, in particular. These genes are transcribed in two successive waves, allowing the development of the arm, then the hand. "We had already discovered that the genes responsible for the hand were controlled by enhancers, specific DNA sequences located in an adjacent area, at one end of the Hoxd cluster. This regulatory domain takes on a different three-dimensional configuration, according to the degree of activity of the enhancers," says Professor Duboule.

Two distinct regulatory domains

In order to understand the molecular processes that preside over arm formation, as well as the transition to wrist and hand formation, the researchers used sophisticated techniques of genetic engineering, molecular biology, and murine embryo cell lines. "Curiously, certain Hoxd genes are involved in the origin of both the arm and the hand, while it is their absence of expression that enables wrist formation," notes Guillaume Andrey, former doctoral student at the Frontiers in Genetics National Research Center and first author of the article.

The biologists demonstrated the existence of a second regulatory domain.

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However, it is responsible for arm development and is located at the other end of the Hoxd gene cluster. They decrypted the complex dialogue established between these genes and the two adjacent domains: "Certain Hoxd genes associate with only one of the two domains, whereas others interact with both, but in different cells and at separate times," explains Guillaume Andrey.

The wrist emerges from a no man's land

During the growth of the limb bud, certain Hoxd genes will shift toward the opposite regulatory domain to establish new contacts. This swing from one domain to the other is the equivalent of a genetic switch, signaling the transition between the creation of the arm and the hand. However, there is an intermediary cellular territory that escapes the two regulatory controls and in which the switch is not activated: this zone will generate the wrist. Thus, the articulation of activities between domains A and B enables the appearance of a mor- phological articulation between our arms and our hands. "The three-dimensional organization of these two regulatory domains, which gives them physical and functional independence, plays an essential role in stimulating the Hoxd genes. These experiments allowed us to demonstrate that there is an additional, topological level of information to modulate gene expression. This is a first!"' says Guillaume Andrey.

More information: "A Switch Between Topological Domains Underlies HoxD Genes Collinearity in Mouse Limbs," by G. Andrey, *Science*, 2013.

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