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Review

Molecular medicine – To be or not to be

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HIGHLIGHTS

- A mutation of hemoglobin inducing Sickle cell anemia is the first molecular disease.
- The atomic structure of proteins opened new perspectives in molecular medicine.
- Protein misfolding is a critical event triggering neurodegenerative diseases.
- The Retromer is involved in the molecular mechanism of several neurological disorders.

GRAPHICAL ABSTRACT

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ABSTRACT

Molecular medicine is founded on the synergy between Chemistry, Physics, Biology and Medicine, with the ambitious goal of tackling diseases from a molecular perspective. This Review aims at retracing a personal outlook of the birth and development of molecular medicine, as well as at highlighting some of the most urgent challenges linked to aging and represented by incurable neurodegenerative diseases caused by protein misfolding. Furthermore, we emphasize the emerging role of the retromer dysfunctions and improper protein sorting in Alzheimer's disease and other important neurological disordered.

Contents

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1. Preamble

The *Great Wave off Kanagawa* by Katsushika Hokusai (1830; Fig. 1), one of the most popular imposing images of Japanese art, has been a source of inspiration to many, including van Gogh and Debussy. The genuflecting fishermen on the boats, more than frantic appear submissive to the immense power of the monster wave, a metaphor of the weakness of human beings *vis-à-vis* the immense force of Nature. In the distance, the sacred Mount Fuji, depicted small but crystal clear seems just about to be engulfed by the wave, yet its perfect conical form may suggest an intervention of beauty in favor of the sailors. Many have interpreted the wide philosophical significance of Hokusai's masterpiece; we feel the image may be a metaphor of the message conveyed by this paper.

2. The Big Bang

Molecular medicine has a father, a mother and a birth date. The father is Linus Pauling, a famous professor of Chemistry at Caltech, Nobel Prize winner for his studies on the chemical bond. The mother is Hemoglobin, the protein of the red blood cells transporting molecular oxygen from the lungs to the tissues. The birth date is November 1st, 1949, when a paper called: "Sickle cell anemia, a molecular disease" appeared in Science [1]. At that moment a new concept was unveiled with the demonstration that a complex and fatal syndrome, the Sickle cell anemia, was caused by the chemical modification of a single well identified protein molecule; and, in agreement with previous indications [2], the molecular mechanism underlying the clinical presentation of the heterozygous and homozygous states became apparent.

The name Sickle cell disease originates from the presence of deformed erythrocytes (Fig. 2) in the venous blood of the carriers. Deformation is associated with altered hydrodynamic rheological properties of the red blood cells and thereby blockage of the circulation in the small peripheral vessels. Painful crisis and necrosis of the tissues would follow, and a number of alterations of different organs become evident as the disease develops, including very serious anemia and mutilations. According to the story, Pauling had the inspiration that a molecular alteration of hemoglobin was the cause of the disease during a dinner conversation with a hematologist from Harvard. The chemical alteration of the protein, called hemoglobin S, was later shown to be the substitution of a single amino acid of the β chains, the Glutamate at position 6 mutated into Valine; two residues out of the 574 amino acids constituting tetrameric hemoglobin are enough [3]. When hemoglobin is deoxygenated, the change of a polar to a hydrophobic amino acid is sufficient to trigger polymerization with intracellular formation of long fibers (Fig. 2) that can grow by interaction with other fibers, leading to deformation of the red blood cells [4,5].

This abnormal human HbS has been the prototype of a genetic disease that, according to a solid interpretation, was the evolutionary response to malaria that has been (and still is) endemic in Africa and the Mediterranean basin. The other well-known genetic abnormality hitting the erythrocytes, called thalassemia, is affecting the relative synthesis of the α and β chains of Hb [6]. In the case of HbS, the mutation of A-to-T in the β globin gene has been fixed in the individual(s) and thus transmitted to the progeny according to Mendel's laws of heredity. It is very interesting that this particular mutation of the β subunit gene was one of the many that must have occurred at random in the human DNA; yet it was quite rapidly stabilized in the black African population because the heterozygote's carrier seems to be endowed with a slightly

Fig. 1. The *Great Wave off Kanagawa* by Katsushika Hokusai (1830).