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MULTI-AUTHOR REVIEW

The biophysics, biochemistry and physiology of CFTR

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When I was a pre-graduated student, there were two ion channels: sodium and potassium channels; these channels were responsible for the action potential, and all other stuff was just leakage. Later on, during my doctorate, many channels appeared; the several types of sodium channels—those of Hodgkin and Huxley and those in the epithelia—and even more classes of potassium channels—perhaps responsible for the membrane potential—were reached by calcium channels; but chloride conductance was still (probably) leakage. It was during my post-doctoral traineeship that chloride channels were taken more seriously, to become the main research object of many excellent laboratories.

In these "heroic" times, when the plethora of channels we know today were identified and characterised, in a memorable issue of Science, Lap-Chee Tsui, Francis Collins and Jack Riordan reported that a protein, termed cystic fibrosis transmembrane conductance regulator (CFTR) is a chloride channel [1–3]. The value of this finding was to provide the molecular basis to understand a lethal genetic disease: cystic fibrosis (CF). It was, indeed, amazing to realize that this new, important molecule is a chloride channel, and thus, an anion channel could be really important. Since then, a lot of different anion channels has been identified; some of them are also related to other genetic diseases, but CFTR is still an excellent benchmark to study—and perhaps to find a good therapy for—a genetic disease from the molecular point of view.

CFTR has several characteristics that render it a quite complex system. This membrane protein belongs to the ABC (ATP binding cassette) protein, but is the only member of this protein family that functions as a channel. CFTR has a unique domain, the regulatory domain, that is not present in other ABC proteins. Noteworthily, there are more than 2000 different mutations on the CFTR gene, that can cause CF, or the congenital absence of the vas deferen, a closely related condition (also present in CF patients).

CFTR is a big membrane protein (1480 amino acids with a molecular weight of 180 kDa), with an amphoteric character and an intrinsically disordered region. Thus, it represents a hard challenge for purification to apply structural studies. Until up today, only two domains, NBD1 and NBD2, have been crystallised [4–7]. Thus, molecular modelling has been used to have an insight into the atomic structure of the CFTR [8–13]. The group of Isabelle Callebaut, in this issue, provides an overview of the theoretical studies including molecular modelling and molecular dynamics (MD) simulations. But, on the other hand, efforts to purify detergent-solubilised CFTR have resulted in promising electron cryomicroscopy data [14–18]. Novel techniques to purify CFTR for structural and physical studies are contributed here by the Bob Ford's group.

The most common mutation in CF, the deletion of a phenylalanine at position 508, involves dramatic alterations of the CFTR traffic, processing and folding [19]. The complex biogenesis of the CFTR is discussed in Carlos Farinha' and Sara Canato's contribution. Protein kinase A (PKA) phosphorylation is the mechanism that

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predominantly regulates the channel gating. Christine Bear's group has shown that PKA phosphorylation is also involved in enhancing trafficking and mediating conformational changes at the interdomain interfaces of CFTR.

As CFTR is folded and docked in the plasma membrane, it works on the anion transport. The complex mechanism of gating of the CFTR channel is described by Oscar Moran in this issue. To fully fill up the functional picture of CFTR, Paul Linsdell presents a consistent description of the ionic pathway of the channel.

CFTR is mainly expressed in polarized epithelia of different organs, having a key role either in ion and water secretion and absorption [20]. Vinciane Saint-Criq and Mike Gray explain, here, how CFTR can play these roles, depending on the organ context. It is, therefore, important to pay attention to the CFTR pharmacology, not only because of the implications on the CF therapy, but, as suggested in Olga Zegarra-Moran' and Luis Galietta's contribution, also for the possibility to use pharmacological modulators of CFTR as promising drugs for a variety of diseases.

Therapy for cystic fibrosis is still an unsolved problem yet. Searching for an optimal CF treatment directly involves the characterisation of the CFTR. Hence, we have done a long analysis where the CFTR is described in various terms: the structure, the biogenesis, the function, either in molecular and systemic perspectives, and how can it be modulated pharmacologically. To keep the way on the effort of looking for solutions for CF patients, this series of basic science reviews are completed with a pure clinical view of the CF, contributed by Carlo Castellani and Benny Assael.

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