Keynote Lectures

K.1

The ubiquitin proteolytic system — from basic mechanisms thru human diseases and onto drug development

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Between the 50s and 80s, most studies in biomedicine focused on the central dogma — the translation of the information coded by DNA to RNA and proteins. Protein degradation was a neglected area, considered to be a non-specific, dead-end process. While it was known that proteins do turn over, the high specificity of the process — where distinct proteins are degraded only at certain time points, or when they are not needed any more, or following denaturation/misfolding when their normal and active counterparts are spared — was not appreciated. The discovery of the lysosome by Christian de Duve did not significantly change this view, as it was clear that this organelle is involved mostly in the degradation of extracellular proteins, and their proteases cannot be substrate-specific. The discovery of the complex cascade of the ubiquitin solved this enigma. It is clear now that degradation of cellular proteins is a highly complex, temporally controlled, and tightly regulated process that plays major roles in a variety of basic cellular processes such as cell cycle and differentiation, communication of the cell with the extracellular environment and maintenance of the cellular quality control. With the multitude of substrates targeted and the myriad processes involved, it is not surprising that aberrations in the pathway have been implicated in the pathogenesis of many diseases, certain malignancies and neurodegeneration among them, and that the system has become a major platform for drug targeting.

K.2

Thoughts about the origin of life and antibiotics resistance

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Ribosomes, the universal cellular machines, act as polymerases that translate the genetic code into proteins with high efficiency. They possess spectacular architecture accompanied by inherent mobility that facilitate their efficient performance although they are essentially RNA enzymes, thus indicating natural mechanisms to turn an inefficient RNA machine into well performing enzyme. The peptide bond formation site is located within a universal internal symmetrical region connecting all of the remote ribosomal features involved in its functions. The elaborate architecture of this region is capable of positioning both the aminoacylated and peptidyl tRNA substrates in stereochemistry required for peptide bond formation, for substrate-mediated catalysis, and for substrate translocation, hence enabling elongation of nascent proteins. The central location of this region, its connectivity to all of the functional features of the ribosome this region indicates its possible key role in intra-ribosome signaling. Its almost full conservation suggests that it is a remnant of a prebiotic RNA machine that is still functioning in the contemporary ribosome. Adjacent to this site is an elongated tunnel, along which nascent chains progress until they emerge out of the ribosome. This tunnel is involved in gating and chaperoning functions; provides the binding site of the first cellular chaperone that encounters the emerging nascent chain, and hosts a major family of antibiotics that target the ribosome. Analysis of the structure of the pocket hosting these antibiotics hints at a possible pathway in the evolution of the species.
Structural biology as a tool for designing drugs against retroviral diseases

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It has been 30 years since the first reports of an epidemic of a new human disease, later called AIDS, have been published. The disease was invariably lethal during the first 15 or so years since its identification, but an unprecedented effort in basic and applied research has led to a development of more than 20 drugs which, in combination, have completely changed the clinical outcome, allowing patients to maintain fairly normal lifespan. This drug development effort was led, to a very large extent, by the success in determining the properties of HIV, the retrovirus responsible for the disease. A very important role was played by structural biology, with the structures of almost all virally-encoded proteins, as well as of some human proteins that play a role in the maintenance of the viral lifecycle, having been solved and made available to drug developers. In particular, the availability of the structures of the three enzymes encoded by the HIV (protease, reverse transcriptase, and integrase) played a major role in creation of a variety of very successful drugs that have changed the outcome of the epidemic, at least in the developed world. The success of designing anti-AIDS drugs was a major boost for structure-based drug design in general, and may also be important for the future work on drugs targeting other pathogens, including emerging retroviruses.