Dictyostelium as a model for human disease

Editorial - Ricardo Escalante

Does it make sense to use a simple organism to study human disease? I am sure that all those scientists using non-mammalian models in biomedical research have faced this question many times, perhaps informally in front of the family and friends or in more critical situations under the scrutiny of grant agencies or evaluation committees. There are obvious arguments supported by the history of science telling us the usefulness of learning from simple models and how this has become essential to understand certain pathologies. In addition to the well-known conservation of genes and molecular pathways among distant species there are practical reasons, such as their simplicity and tractability compared with the complexity and the experimental inaccessibility of the human body. An added value from the studies of simple models is that, not infrequently, they open radically new perspectives in the study of a given pathology. This is often the result of applying unbiased genetic analysis and the opportunity in a model organism to address the function of a given gene in the organism as a whole. As a consequence, this research might not be translated immediately to human disease but serve as a ground for more applied approaches. As Louis Pasteur stated “There does not exist a category of science to which one can give the name applied science. There are sciences and the applications of science, bound together as the fruit of the tree which bears it”. This series of reviews exemplifies beautifully howthe social amoeba Dictyostelium fulfills all the requirements for a useful experimental model in understanding the basic principles of human disease.

The Dictyostelium life style provides excellent opportunities to address disease-related processes in a meaningful way. This soil amoeba predates bacteria in its natural environment. As a result of this selective pressure, bacteria developed strategies to survive which later were used and adapted to infect other organisms including humans. The reviews by Michael Steinert and Wanessa Lima et al. describe the use of Dictyostelium as a model to study the interaction with several pathogens of immense importance in human health such as Legionella, Mycobacterium and Pseudomonas.

Social amoebae use motility and chemotaxis both to hunt bacteria and to aggregate collectively to form amulticellular organism. The underlying mechanisms driving these phenomena are essentially similar to those of mammalian cells, and thus Dictyostelium has become a prominent model in this field. Michael Carnell and Robert Insall review how research in Dictyostelium has contributed to our understanding of cell motility-related pathologies which includes deficiencies in the immune and neurological systems. One of these deficiencies is Lissencephaly, a severe brain disease caused by mutations in highly conserved genes present in Dictyostelium, LIS1 and DCX. The molecular roles of these proteins and others involved in this pathology are now beginning to be understood thanks in part to Dictyostelium. Irene Meyer et al. review our current knowledge of the molecular clues underlying Lissencephaly and describe invaluable new findings on the function of the Dictyostelium DCX protein.

Dictyostelium has also proved its usefulness in pharmacogenomics helping to unveil the mechanism of action of certain drugs and at the same time to reduce the use of animals in research. Two wonderful topics have been reviewed in this issue. Stephen and Hannah Alexander explain how the isolation of a Dictyostelium mutant resistant to the cancer chemotherapeutic drug cysplatin prompted further studies in human cells on the role of sphingolipids and ceramide in regulating the response to this drug. Likewise, the review by Marthe Ludtmann et al. highlights our current knowledge of the mechanism of action of two commonly used bipolar disorder treatments (valproic acid and lithium).

Human diseases associated with the endocytic and secretory pathway, such as Chediak Higashi Syndrome, Ceroid Lipofuscinosis and Niemann Pick Disease, originate severe symptoms affecting multiple organs and compromising the lifespan of affected patients. Markus Maniak here reviews current research in Dictyostelium related to the molecular basis of these complex diseases. Finally, Lisa Francione et al. address the complexity of the mitochondrial diseases and how the simplicity of Dictyostelium can help to uncover certain aspects of the cytopathological pathways involved.

I hope this series of reviews will excite your curiosity and serve as a ground for further research using Dictyostelium as a model of human disease. It would also be gratifying if they help to convince those not working with simple models that this kind of research does indeed make sense.

Also, Dictyostelium has been used to help identify targets for drugs used to treat human diseases: cis-platin, an anticancer agent (Li et al. 2000); lithium used to treat bipolar disorder (Williams et al. 1999); and bisphosphonates used to treat osteoporosis (Grove et al.Â As a â€œprofessionalâ€ phagocyte, with well-founded cell and molecular biology, Dictyostelium provides a model both for the natural protozoan host and for the alternate host: the human macrophage. This is now a major field of research that is comprehensively reviewed elsewhere (Steinert and Heuner 2005; Bozzaro et al. 2008; Bruhn and Steinert 2008; Cosson and Soldati 2008; Clarke 2010) so I will give only an overview. Dictyostelium might be an outstanding eukaryotic cell model for deciphering the utmost challenging problem of EV heterogeneity, and for unraveling the still mostly unknown mechanisms of their specic functions as mediators of intercellular communication. Keywords: extracellular vesicles; microvesicles; exosomes; oncosomes; apoptotic bodies; intercellular communication; human disease; cancer; Dictyostelium discoideum. 1. Introduction.Â EVs are quite appealing for future theranostics (diagnosis, prognosis, and therapy) of human diseases, and especially cancer. Dictyostelium discoideumâ€”a model for many reasons.Â Reddy AK, Balne PK, Garg P, et al. Dictyostelium polycephalum Infection of Human Cornea. Emerging Infectious Diseases. 2010;16(10):1644-1645. doi:10.3201/eid1610.100717. APA. Reddy, A. K., Balne, P. K., Garg, P., Sangwan, V. S., Das, M., Krishna, P. V....Vemuganti, G. K. (2010). Dictyostelium polycephalum Infection of Human Cornea. Emerging Infectious Diseases, 16(10), 1644-1645. https://doi.org/10.3201/eid1610.100717. Close. Dictyostelium is recognized as an excellent model system for studying human neurological disorders, including epilepsy, lissencephaly, Parkinsonâ€™s disease, Alzheimerâ€™s disease, and Huntingtonâ€™s disease [6â€“10]. Dictyostelium also contains the highest content of prion-like proteins of all organisms investigated to date [11, 12]. Dictyostelium amoebae inhabit forest soil and consume bacteria and yeast, which they track by chemotaxis. Starvation, however, prompts the solitary cells to aggregate and develop as a true multicellular organism, producing a fruiting body comprised of a cellular, cellulosic stalk supporting a bolus of spores. Thus, Dictyostelium has evolved mechanisms that direct the differentiation of a homogeneous population of cells into distinct cell types, regulate the proportions between tissues and orchestrate the construction of an effective structure for the dispersal of spores4. Many of the genes necessary for these processes in Dictyostelium were also inherited by Metazoa and fashioned through evolution for use within many different modes of development.