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Editorial

EDITORIAL

Serendipity in senescence

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Serendipity can bring fun to experimental physiology. It often arises from individuals who barely know each other having a "coffee room" or "water cooler" conversation. Research laboratory buildings are sometimes designed to promulgate such interactions, but of course also required is a basic level of inquisition and respect among colleagues in disparate fields. The recently opened Vollum Institute of Oregon Health Sciences University had such a "coffee room," strategically situated to catch cross-traffic from neighboring research buildings adjacent to the Institute itself. Although I was not a frequent partaker, one day I bumped into a virologist from one of the basic medical science departments. David Kabat studied ecotropic retroviruses.

If I had ever known what a retrovirus was, then I had long forgotten. He explained that some of them caused leukemia. And as for ecotropic, this sent me straight to the dictionary. At that time (about 1990) my group was studying potassium channels, either in brain neurons of by cloning and expressing them. Part of this was a wonderful collaboration with another recently hired Vollum Institute scientist, the molecular biologist John Adelman. Our collaboration rested heavily on oocyte expression, driven largely by the efforts of postdoctoral fellow Michael Kavanaugh.

A cDNA had been cloned by James Cunningham's group at Harvard, which conferred susceptibility to infection by a mouse ecotropic retrovirus.[1] Dave Kabat wanted to express the cDNA gene in oocytes to make some protein so as to make antibodies to the virus receptor, and wondered if we might help with that. We did that for him, and the injected oocytes bound the viral envelope protein. When I asked him what kind of protein the receptor it was, he replied that no-one really knew, but that it was very hydrophobic with as many as 14 potential membrane-spanning domains. The channels with which we were familiar (potassium, sodium, and calcium) at that time had six or 24 (four repeats of six) transmembrane domains, so they did not seem like obvious candidates. A Na–glucose cotransporter had been cloned a few months earlier by Ernie Wright's group[2], which was thought to have 10 or 11 transmembrane domains, but the retrovirus receptor had no sequence relatedness to that or any other membrane protein.

We were relative neophytes in oocyte expression, and we had heard that the addition of horse serum helped to maintain their health. One day, when Mike Kavanaugh added horse serum he noticed a small but reproducible inward current, but then realized that it was only seen in the oocytes that had been injected with the ecotropic retrovirus RNA. Wondering what might cause the inward current, Mike next tried modified Eagle's medium, and quite soon thereafter identified the amino acid lysine as being responsible. We measured the uptake of lysine (in coulombs) by the inward current that flowed when lysine was applied for several seconds, and we also measured the uptake of tritiated lysine (in moles) when it was applied to the oocytes for a few minutes and then washed away. It was a moment of profound satisfaction when we calculated the correspondence of 96 500 coulombs/mole[3]. The Faraday constant had been burned into my cerebrum since early learning (and subsequent teaching) of cellular biophysics!

A few further experiments showed that the transporter recognized other positively charged amino acids (arginine, ornithine, and histidine).[3] Some neutral amino acids were also transported, such as homoserine, but that required the presence of sodium ions whereas uptake of the basic amino acids did not.[3] The literature took us at once to the extensive work of Halvor Christensen and the realization that "our" new transporter had been extensively characterized more than 20 yr before in physiological experiments[4] and named system y^+. Christensen later wrote of our work: "the finding has been hailed as a landmark in cell physiology which reveals new mechanisms of viral pathogenesis. The studies represent the first amino-acid transporter to be cloned, as well as the first example of a virus subverting a transmembrane protein as a receptor."[5]

But the serendipitous fun did not end there. At the time of this work at the Vollum Institute I was a member of the Editorial Board of the Journal of Physiology, and after one of its meetings the Board was enjoying dinner as guests of Pembroke College, Oxford. Quite by chance I found myself sitting beside Richard Boyd, a college fellow and physiologist. We had not met before, and he kindly explained to me something of his own research,

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which dealt with membrane transporters, particularly system y^+. He seemed utterly astonished when I mentioned to him our paper in press and that "we had just cloned that transporter." Within months Richard was visiting us in Oregon for potential collaboration. He later concluded a scholarly review[6] by writing "future studies will require.... more importantly, an open mind to accept that lessons in transport may be coming from unexpected and diverse disciplines."

There quickly followed the identification of other membrane proteins as routes for virus entry into cells, most notably the chemokine receptor CCR5 (along with CD4) for human immunodeficiency virus (HIV)[7] and a sodium-dependent phosphate transporter for gibbon ape leukemia virus.[8] And Mike Kavanaugh continued his highly productive study of transporters as an independent investigator.[8]

Our 1991 paper[3] was accompanied by *News and Views* by Robin Weiss[9] concluding that "[the work] indicates moreover that an alliance between cellular physiologists and virologists might pay handsome dividends...." The energetic facilitation of such alliances will become ever more necessary if we wish to stave off the inevitable senescence of serendipity.

Conflicts of interest

None declared.

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