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Commentary

HISTORY

Susan Lindquist (1949–2016), Phenomenal Scientist and Insufficiently Acknowledged Contributor to Evolutionary Medicine

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Abstract Susan Lindquist studied diverse aspects of the cellular control of protein folding and how it could go wrong, potentially leading to dysfunction and disease. Her innovative studies suggested new mechanisms relevant to the inheritance of cellular traits and to evolutionary pathways. Although she did not directly identify with the evolutionary medicine community, her body of work is highly relevant to this field and deserves a wide audience among those interested in the ways in which evolution is relevant for medicine.

Keywords Susan Lindquist; heat-shock proteins; chaperone; protein folding; heat shock protein 90 (Hsp90); fruit fly; yeast; *Saccharomyces cerevisiae*; cavefish; *Arabidopsis thaliana*; capacitor for evolution; genetic variant; genotype; phenotype; inheritance; cell biology; therapy; cancer; prion; neurodegenerative disease; tumorigenesis; heat shock factor 1 (HSF1); neurofibromatosis type 1 (NF1)

In 2016, I called attention to a number of investigators who between roughly 1940 and 1990 made major contributions to biomedical science, and in some cases clinical medicine [1]. The work of these scientists involved ideas or methods related to evolutionary biology but the often seminal findings and insights produced by these individuals are not generally discussed or recognized in official evolution and medicine circles, perhaps accounting for the perception that after an initial burst of activity early in the twentieth century, there was a period of virtually no relevant work in evolutionary medicine. What may partly account for the relative obscurity of these scientists and their insights into how evolution impinges on medicine, among self-identified members of the evolution and medicine community, is that these scientists did not explicitly present themselves as participants in a distinct community devoted to evolutionary medicine.

This disconnect did not completely end in 1991, which some suggest is the start date of modern "Darwinian medicine" [2]. Below, I provide an example of a scientist active until last year who exemplified the continuation of this phenomenon. Susan Lindquist, who passed away last October, had a spectacular biomedical research career [3, 4, 5, 6], in which she generated a number of novel and potentially seminal concepts and observations relating to both evolution and disease.

Lindquist began her research career in the lab of Matthew Meselson at Harvard in 1971 just after graduating with bachelor's degree in microbiology from the University of Illinois. Her Ph.D. thesis studies described proteins in fruit flies that mediate the heat shock response. These molecules, typically referred to as heat shock proteins, were eventually demonstrated to be chaperones, that is, gene products that assist other proteins in folding into their functional conformations.

In 1976, Lindquist moved to the University of Chicago for post-doctoral training with Hewson Swift, who studied genome organization in a number of organisms. She obtained her first faculty position there in 1978. Finally, Lindquist moved to the Whitehead Institute for Biomedical Research and MIT in 2001, where she remained until her untimely death. She served as a director of the Whitehead Institute from 2001 to 2004.

After moving to Chicago, Lindquist proceeded to focus her research on heat shock proteins in yeast despite advice from other faculty members not to switch organisms. Her rationale for shifting the direction of the lab to yeast was dominated by her recognition of the substantially greater facility for doing genetics and genetic manipulation in yeast. The future largely vindicated her intuition with respect to this major career decision.

Over the next 35 years, the Lindquist lab continued to study the fundamental relevance of protein folding and misfolding in cell function, inheritance, evolution, and disease. These studies continued in yeast but also in fruit flies and many other organisms, including humans.

Lindquist published numerous papers of high impact. The exceptional creativity and significance of her work was recognized by a variety of honors and awards, such as being

elected to the National Academy of Sciences, the National Academy of Medicine, and the American Academy of Arts and Sciences. She was also the recipient of major scientific awards such as the Presidential National Medal of Science, the E.B. Wilson Award, and the Otto Warburg Prize. Lindquist became an investigator of the Howard Hughes Medical Institute beginning in 1988.

I became interested in Lindquist's work when I encountered her notion that a heat shock protein, Hsp90, by virtue of its ability to assist the folding process for other cellular proteins (i.e., a protein chaperone) could serve to permit genetic variation to accumulate to a greater extent than would otherwise be the case; see Rutherford and Lindquist's study in [7]. In this study, they found that heterozygosity for a mutant form of the Hsp90 gene that decreased chaperone function revealed diverse morphologic variants in different fruit flies. These alterations were demonstrated to arise from multiple, previously unrecognized genetic variants for which the associated phenotypic effects were suppressed by the ability of Hsp90 to limit the impact on conformation of amino acid substitutions in the corresponding proteins.

Based on the above results, the authors proposed that Hsp90 functioned as a "capacitor" for evolution, permitting genetic variants to accumulate without substantial phenotypic effects until environmental factors, such as elevated temperature, reduce Hsp90 functional supply, which is not strongly increased by higher temperature, relative to cellular protein demand. The resulting mismatch in chaperone activity and need permits variant proteins to fold somewhat differently and express new phenotypes that can then be subjected to selection. Continuing selection for the traits associated with these variants could favor additional mutations in the relevant genes that render them independent of the magnitude of Hsp90 chaperone function. Further investigation extended these phenomena to other species [8,9] and added support to their possible relevance for organismal evolution [9]. Lindquist along with her lab associates and collaborators found ways to apply their insights into these Hsp90-related phenomena to overcoming drug resistance and improving pharmacologic therapy for infections by the fungal pathogen Candida albicans [10].

Specifically, Lindquist reasoned that Hsp90 chaperone activity might facilitate the continued functioning of fungal proteins that happened to have pre-existing amino acid substitutions (relative to the corresponding wild-type proteins) limiting inhibition by antifungal agents. Therefore, in the presence of an antifungal agent, inhibiting Hsp90 might be expected to potentiate the toxicity to the fungal cells of the therapeutic drug. Results presented in the cited study provide support for the reasoning behind this novel approach. Similar insights may also prove relevant for overcoming the resistance of cancer cells to molecularly targeted therapeutic agents.

Another line of investigation of the Lindquist lab that eventually caught my attention was devoted to exploring the role of prion-like proteins in yeast. After Lindquist et al. initiated this work in 1995 [11], following the report in [12] by Reed Wickner that a prion-like protein could explain a case of cytoplasmic inheritance in the yeast *Saccharomyces cerevisiae*, some may have wondered whether studying prions in yeast was likely to lead to insights useful for understanding human neuropathology caused by prions. Lindquist and her colleagues persevered and revealed why any doubters were wrong. In addition, this work established a mechanism for cellular inheritance of phenotypes that depended primarily on protein conformation as opposed to nucleic acid.

In 2012, Halfmann et al. showed that prionic proteins could be found in wild yeast strains [13]. In a subsequent paper, Holmes et al. demonstrated that a transcriptional repressor in *S. cerevisiae* could adopt a prionic state thereby initiating a physiologic response (e.g., facultative multicellularlity) to environmental conditions [14]. So for example, exposure to ethanol at concentrations achieved in wine fermentation resulted in prion formation of the transcriptional repressor and derepression of a gene encoding a protein critical for cell-cell adhesion, that is, the transcription factor was being recruited off of the DNA and binding to other copies of the same protein.

Arguably, this line of investigation has implications for cell biology, biochemistry, genetics, evolution, and clinical medicine.

Lindquist also published a series of papers demonstrating that the transcriptional regulator of the response to heat shock and other stressors, heat shock factor 1 (HSF1), additionally plays a role in tumorigenesis. Support for this novel claim included demonstrating that homozygous HSF1 deletion protected mice from chemically-induced carcinogenesis or carcinogenesis related to mutations in the tumor suppressor gene, p53. In additional studies, Lindquist and colleagues (1) explored the potential of using inhibitors of HSF1 to impede the development of cancer, (2) demonstrated that HSF1 controlled genes involved in many cellular processes relevant to malignant transformation and that these genes were partly distinct from those involved in the heat shock response, and (3) demonstrated that loss of the tumor suppressor neurofibromatosis 1 (NF1) promotes carcinogenesis mediated by HSF1 [15,16,17,18].

I have not attempted to be comprehensive, so the articles cited above give only a small but I hope somewhat representative sample of the extensive contributions Lindquist made to biomedical research. Along with other papers on issues of protein folding and chaperone function in human disease, Lindquist and her associates published a number of studies in addition to those cited above directly relating to the effort to improve therapy for cancer and other diseases [19,20,21].

Despite the extraordinary research accomplishments of Lindquist; her training of over 100 postdoctoral fellows, graduate students, and undergraduates; her leadership positions; and extensive list of awards and honors, she has not to my knowledge been mentioned in any of the conference sessions devoted to evolution and medicine that I have attended over the past 10 or so years. Furthermore, I have not seen citations to her work in the books I have read on evolution and medicine. The example of Susan Lindquist suggests that members of the evolutionary medicine community should consider broadening the range of work they follow, discuss, and include under the rubric of evolutionary medicine and public health.

Conflict of interest The author declares that he has no conflict of interest.

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