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OVERVIEW

Why Nuclei?

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Why do cells have nuclei? Prokaryotes, by far the most abundant life forms, do just fine without one. Answers to this question will consist of equal measures of uncertainty and speculation. However, the exercise is nevertheless worthwhile since it may illuminate some elusive principles in cell biology.

The current guess is that single cell eukaryotes appeared perhaps a billion years ago. Although this date is incredibly ancient, it is still long after the postulated appearance of the first recognizable prokaryotes—perhaps 1.5 to two billion years in the past. Some have asked why it took so long for nuclei to appear—such questions show innocence of nuclear structure. The extraordinary design of nuclei ought to make one wonder how such an organelle came to be at all. Nuclei are highly complex and specialized in function; their appearance in evolution was not a quirk but required an incredibly difficult evolutionary step. The driving force for such a step must have been the conferring of a truly powerful advantage. (I, for one, cannot credit suggestions of a simple origin as the remnants of one ancestral cell engulfing another. Nuclei do not in the least suggest a cannibalized prokaryotic progenitor.)

Perhaps we should ask first what great advantage could the early nuclei confer. Conventional biochemistry cannot help us since its major focus, metabolism, differs little in prokaryotes and eukaryotes (making our metabolic pathway wall charts almost universal). We may surmise from modern descendants that the first eukaryotes introduced complex, dynamic organism form, presumably for predation, as an evolutionary strategy. Contemporary eukaryotes show marvels of complex and specialized form developed at the single cell level.

The appearance of life forms specialized for predation must have despoiled the pre-Cambrian seas. The prokaryotes, bacteria, and blue green algea, forming a soup of the primeval oceans and swamps, would have been helpless against an onslaught of the single cell equivalent of jaws and legs. Chemical agents, elaborate toxins and the like, the weapons of prokaryotes, could offer no effective defense against predators that could swim and grasp.

Given that complex form facilitated predation, why should it require segregation of genetic material into a separate nuclear compartment. We can try to guess intelligently. Again, contemporary forms of the unicellular eukaryotes suggest they had a major increase in DNA content compared to prokaryotes. Breaking this DNA into manageable packets, such as chromosomes, might well have exceeded the capabilities of prokaryotic machinery for DNA replication and cell division. The nucleus affords elegant solutions to these managerial problems. There are, however, more compelling reasons for segregating DNA away from the cytoplasm.

The eukaryotes saw the introduction of complex and active cytoplasmic machinery. The functions and structure of eukaryotic cytoskeletons were probably incompatible with the loose packing of DNA afforded by prokaryotic nucleoids. Put simply, DNA in the cytoplasmic space could never be kept from entangling the struts of the cytoskeleton and it had to be kept from jamming the works. (Mitosis is a special case in which chromatin is exposed to the cytoplasm but only when very tightly bundled into the chromosome.)

The protista and metazoa both depart markedly from the simple structural plans of bacteria and blue-green algae and devote large amounts of genetic information to the specification of architectural complexity. Translating this information into complex structure required a significant change in the mechanism of protein synthesis. In metazoan eukaryotes, and by inference, in all eukaryotes, proteins destined for cell structure proteins are not synthesized randomly in space but at sites topologically linked to assembling structures. A single protein may very well be synthesized at many sites throughout the

cytoplasm. mRNA synthesized at one locus in the nucleus must be parceled out onto polysomes whose location is fixed by their attachment to the cytoskeleton. Bacteria, by virtue of their much simpler physical organization, apparently can make do with proteins made only at the site of transcription. This simple strategy seems to doom the prokaryote to remain small and structurally simple while even single nucleated cells can be complex organisms large enough to see with the naked eye. Of course, the nucleated cell reaches its apotheosis in the true multicellular organisms such as redwoods and blue whales.

If the reasoning here approximates reality, the first nuclei served to manage vastly increased amounts of DNA and keep it from entangling dynamic cytoplasmic structures. Once transcription and translation were separated, mRNA for structural proteins could be parceled out to the many different sites where the complex structure was assembling. Apparently, many variations on this theme are possible; single celled eukaryotes show an immense variety of nuclear forms and spectacularly different versions of mitosis.

Although it superficially resembles protistan nuclei, the metazoan nucleus is very different in functions and appears to have a more complex internal organization. Compared to the single cell organisms, nuclear form and mitotic strategies in the metazoa and metaphyta are relatively limited in variation (see Georgatos, page 69, this issue).

Protistan nuclei are surely the much older, formed in the very dim past, long before the nuclear matrix allows responses to physical properties of cells such as shape. It confers upon the nucleus mechanical properties such as internal rigidity (i.e., a relatively large bulk modulus) which prevents the nucleus from simply deforming in response to cytoskeletal tensions. The few minor efforts to image a nuclear matrix in protistan nuclei suggest that it is much less developed in these earlier organisms. The mechanical rigidity of the interphase nucleus is suggested by time lapse micrography; the nucleus appears as an island of utter calm in the surrounding sea of roiling cytoplasm. Intermediate filaments can probably serve as mechanical connections to the cell surface. These are the most stable of the major filament systems and many terminate on and couple to the nuclear lamina.

The nuclear matrix serves yet another function unique to the metazoa and metaphyta—maintaining the tissue specific organization of chromatin into active euchromatic regions and apparently silent heterochromatin. The absence of an equivalent function in single celled animals is not due to smaller amounts of DNA. The DNA content of some forms, such as dinoflagelates, can be as high as in mammals. The ability to reorganize chromatin throughout the organism is very specific to and necessary for metazoan multicellularity. This capacity implies a much more complex nuclear matrix than might be found in the protista.

To summarize briefly, nuclei probably appeared coincident with the first appearance of structural complexity in single celled organisms—first at the single cell level and later in the metazoa and metaphyta. The first nuclei probably developed to manage a much greater amount of DNA, arrange for its orderly replication and keep it out of the way of complex and dynamic cytoplasmic machinery. Most importantly, the physical separation of transcription and translation allows mRNA to be parceled out by ancillary mechanisms to different sites of structure assembly in the cytoplasm. The evolution of true multicellular organisms, such as ourselves, required further refinement of the nucleus by development of a highly complex nuclear matrix. The relative rigidity of this matrix is necessary for cells in tissue to respond to mechanical signals from its neighbors. The complexity of the metazoan matrix reflects its multiplicity of functions in the general organization of chromatin and in the tissue specific transcription of genetic information.

The series that follows is, in some regards, a landmark since much of the presented material reflects the recent knowledge of nuclear structure. This is especially true of the contribution by Stein et al. (see page 4, this issue) which is a ground breaking exploration of the relation of nuclear architecture and regulatory signals. Getzenberg (see page 22, this issue) addresses the old puzzle about how the same signal has such different results in different tissues. He suggests this is due to differences in chromatin architecture deriving from changes in the nuclear matrix which, in turn, are reflected in changes in nuclear matrix protein composition. The topic of nuclear matrix protein composition promises to be of considerable future interest since it has

clinically significant consequences. The contribution by Davie and Hendzel (see page 98, this issue) shows the nuclear matrix localization and, by inference, the spatial localization of acetylase enzymes that operate directly on the nucleosomes of chromatin. The contribution of Georgatos reminds us that metezoan nuclei remain capable of surprising forms.