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Perspective Article

Hylonome

The secret life of bone cells

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The primatologist, Clarence Ray Carpenter, was my teacher, my inspiration and a downright hero to me. Many consider him the father of modern primatology. Whatever! What is certain is that he had an extraordinary career. One of his lifetime interests was in how animals (and people) communicated. One of his many innovations was so simple it was revolutionary. He studied primates in their natural environment. Through the efforts of National Geographic, we are all familiar with Jane Goodall and Dian Fossey and others. And, their work is important. But, they would have been the first to admit that it was Carpenter's careful observations of the black howler of Central America, the gibbon of Southeast Asia, and orangutan of Indonesia, that set the standard. No, he wasn't against technology; it was all about how it was applicated. He pioneered the innovative use of technology, including motion picture and sound recording in the field. He convinced the world that understanding natural behavior in an artificial setting (e.g., laboratory or zoo) revealed little about normal behavior.

The concept of natural environment is equally relevant to bone biology. The thesis of this presentation is that careful observation of the cells that produce and destroy bone tissue in their natural surroundings and their interactions with neighboring cells can lead to a greater understanding of how the intricate architecture of bone is created and maintained, and in addition, is fun. Tools for accomplishing this goal are numerous and becoming even more powerful, but are incredibly under-utilized. It is a sad fact that very few scientists in our field bother to observe bone cells in their natural context.

Looking through a microscope at skeletal tissue is pure delight. Visible light, fluorescence, electron, they are all wonderful. The more you look, the more you see. The more you see, the more you realize some of our cherished concepts about how bone grows, organizes itself and responds to its physical and chemical environment are, at best, first order approximations. There are a great many important relationships that need to be investigated. Here are a few:

Team work

One of the most obvious differences between cultured cells from bone and bone cells *in situ* is the much higher level of organization of the latter. This *in vivo* organization results in the coordinated production of bone matrix by osteoblasts. These cells do not function as individuals; they function as a team. How osteoblasts communicate with one another and coordinate their activities to produce lamellar bone is a great mystery.

What am I?

Osteoblasts have a plastic phenotype. At one extreme they appear as plump cells with an accentric nucleus and a prominent golgi-apparatus. When viewed by transmission electron microscopy an extensive system of rough endoplasmic reticulum and numerous mitochondria are observed. At the other extreme, osteoblasts exhibit the lining cell phenotype. Lining cells are much smaller, flatter and are much less well-endowed with organelles associated with protein synthesis, trafficking, and secretion. It is obvious that the lining cell produces little if any bone matrix but these cells which generally outnumber osteoblasts are likely to play a key role in mechanical signal transduction as well as response to systemic factors. The phenotypic appearance of an osteoblast is a continuum; intermediates between osteoblasts and lining cells are readily apparent. Often every stage is observed within a single modeling/remodeling site. There is every reason to believe that the phenotypic appearance of an osteoblast is tightly regulated and that these cells can be rapidly modulated from one appearance to another. The mechanisms that regulate the process are critically important to bone balance and are unknown.

Size counts?

Osteoblasts vary in size in a predictable manner, at least in rats. During growth, endocortical osteoblasts are larger than osteoblasts on cancellous bone surfaces. Osteoblasts decrease

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in size with age. Osteoblast size and activity may be closely associated but this relationship has not been studied. It would be of great interest to know whether osteoblast size plays a role in contributing to genetic differences in bone mass.

It's in the blood (vessel)

The differentiation of osteoblasts and osteoclasts have been studied ad nausia. And, we can make it happen in the dish. But, we don't get bone there; at least nothing I can recognize as such. Why not? I really do not know. However, I see things through the microscope that might provide hints.

When you see an osteoclast in its natural environment, a blood vessel is in close proximity. This is most easily seen at the base of the growth plate during endochondral ossification and during Haversian remodeling of cortical bone. But, it is also true during endocortical and cancellous modeling and remodeling. Can it be that angiogenesis plays an essential role in directing bone growth and turnover? Some of the most important natural regulators of bone growth and turnover (e.g., estrogen) regulate angiogenesis. I am very surprised that this concept has largely escaped the attention of the pharmaceutical industry.

Where did I come from and where am I going?

The classic model of osteoblast differentiation describes an orderly progression of multi-potential precursors through several intermediate cell types and finally to mature osteoblasts and then to osteocytes or cell death. This sequence can be observed in the periosteum of growing bones. However, no such sequence is observed during Haversian remodeling, endochondral ossification and ectopic ossification. At these sites, osteoblasts appear to differentiate from cells associated with the vasculature. In certain pathological situations, osteoblasts can originate from fibroblasts. Finally, osteoblasts can be recruited by a process I call modulation. Modulation from the lining cell phenotype to the osteoblast phenotype, in contrast to differentiation, does not require cell proliferation.

Neighbors

The most stringent classification of a bone cell is to limit consideration to cells that either produce bone (osteoblasts), are derived from osteoblasts (lining cells and osteocytes) or remove bone (osteoclasts). The attractiveness of simplicity notwithstanding, this classification is of minimal value in helping us understand the complexities of the skeleton. Indeed, production of bone matrix is likely to be only one function of the osteoblast and these cells may only perform this activity during a limited portion of their lifespan. As previously mentioned, another function of osteoblast lineage cells (osteoblasts, bone lining cells and osteocytes) is signal tranduction in response to mechanical and hormonal signals.

A less stringent classification is to consider all cells on and within bone. The problem with casting the net this far is that it is likely to include cells that have nothing to do with the creation and maintenance of the skeleton. The compromise position is to include cells that produce and destroy bone, as well as cells located on (e.g., bone lining cell), within (e.g., osteocyte), and in the proximity of bone surfaces that regulate activity and/or number of osteoblasts and osteoclasts. A great deal of effort is needed to identify and to characterize the role of these accessory cells.

The mast cell is a great example of an accessory cell. Mast cells are living drug factories that produce and release a multitude of chemicals that influence bone cells. Mast cell excess, as well as deficiency, is associated with bone disease.

Epilogue

The *in situ* investigation of bone will continue to delight and reward those who trouble to look and formulate questions based on what they see.