Chapter 18

Web Text Box 4

Control of cell number:
Why are we bigger than a mouse and smaller than an elephant?

Animal species generally exhibit a limited size range. The striking exception is the domestic dog (think of the chihuahua and the great dane) but this is the result of several centuries of intensive breeding. Humans vary in size but this is largely due to differences in the length of our bones or the amount of body fat: by and large we are made up of similar numbers of cells. No one would dispute that humans are made up of more cells than a mouse (and, hence, are the result of more cell cycles) and less than an elephant. How are these differences achieved? Why don't humans grow to be the size of elephants or whales? No one really knows the answer but an important clue has emerged from the study of a cyclin dependent protein kinase inhibitor called $p27^{KIP1}$. As we describe on book page 306, p27 binds to and inhibits G1 CDKs in response to cell-cell contact. For as long as human cells have been grown in culture researchers have noted that when cells come together to form a confluent layer on the bottom of the culture dish no more cell divisions take place. This phenomenon is known as contact inhibition. It turns out that cell-cell contact triggers the appearance of p27 which shuts down the division machinery. Cancer cells that do not produce p27 do not exhibit such restrained behavior and pile on top of one another in an unseemly scrum.

A new role for p27 emerged from the creation of knockout mice that are unable to produce the protein. p27-/p27- (i.e., lacking both copies of the gene) mice are up to 40% bigger than their p27+/p27+ littermates. The modified mice are not fatter but, rather, contain more cells. In other words the signal to stop growing at a certain size has been lost, at least in part. However, the enlarged mice form multiple tumors because the loss of the developmental ‘stop’ signal also applies to the growth of internal organs. So bigger is not always better.

Coincidentally, the recent sequencing of the dog genome has shed light on why man's best friend shows such size variation, albeit unnatural. The answer lies in the gene IGF1 that encodes insulin-like growth factor. As its name suggests, the protein is a hormone related to insulin but which acts to cause cells to divide rather than to utilize and store glucose. Almost all the variation in size between different dog breeds can be attributed to differences in the IGF-1 gene.