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The Progress Zone Model for specifying Positional Information

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ABSTRACT The Progress Zone Model proposes that positional information in a growing system can be specified by the time the cells spend in a zone where growth occurs. In the vertebrate limb, the Progress Zone is specified by the Apical Ectodermal Ridge. The best evidence for the model is that killing cells in the zone at an early stage leads to loss of proximal structure as cells remain much longer in the zone as it becomes repopulated.

KEY WORDS: *progress zone, positional information, limb development*

One common mechanism for specifying pattern in a developing system is that based on positional information; the cells acquire a positional identity with respect to boundaries and then interpret this positional value by changing their state which can lead to further differentiation, change in shape or cell division. In the developing vertebrate limb a signal from the polarizing region – sonic hedgehog – sets up a gradient that specifies the antero-posterior axis. Thus digit 4 in the chick limb is specified at high value and digit 2 at a low value being further away from the polarizing region.

For the proximo-distal axis we have proposed a model based on time for specifying positional information. This mechanism is particularly appropriate for a growing system like the extension of the limb bud and the formation of the cartilaginous elements from humerus to the tips of the digits. Another relevant growing system is that of the specification of positional values, represented by the *Hox* genes along the antero -posterior axis of the embryo as the node regresses and somites form. The proposed mechanism uses timing to generate a gradient rather than a positional signal from a source. Thus, as the limb bud grows out, the cells increasing positional valued could be specified at the tip.

More specifically we suggest that the apical ectodermal ridge at the tip of the limb specifies a progress zone about 300 microns from the ridge, though the molecular basis remains unknown. The progress zone is where the cells acquire their positional value. They do this by measuring the time they spend in this zone - their clock stops when they leave the zone which they continually do as all the cells in the zone are dividing (Fig. 1). Thus the cells that come out last form the digits.

Removing the ridge results in the loss of the progress zone due to the lack of a signal from the ridge and also some cell death, thus when it is removed early there is truncation of the limb. By contrast if cells in the progress zone are killed, by for example, x-irradiation at an early stage, the distal structures develop and proximal ones are lost. This is the best evidence for the model for cell loss requires the remaining cells in the progress zone to repopulate it before cells begin to leave it. Thus very few cells spend just a short time in the zone and thus proximal structures cannot develop. Our evidence from ridge removal suggests that each cartilaginous is initially the same size as the progress zone - that is the result of sufficient cell divisions to extrude its volume; the size differences in the elements is due to their growing differently. Thus there are seven cell cycles and seven elements along the axis. A prediction from the model is that reducing the size of the progress zone should result in a normal limb, but all the elements would be smaller as the number of cells coming out in each unit of time will be smaller. It is encouraging that a progress zone mechanism has now been proposed for the

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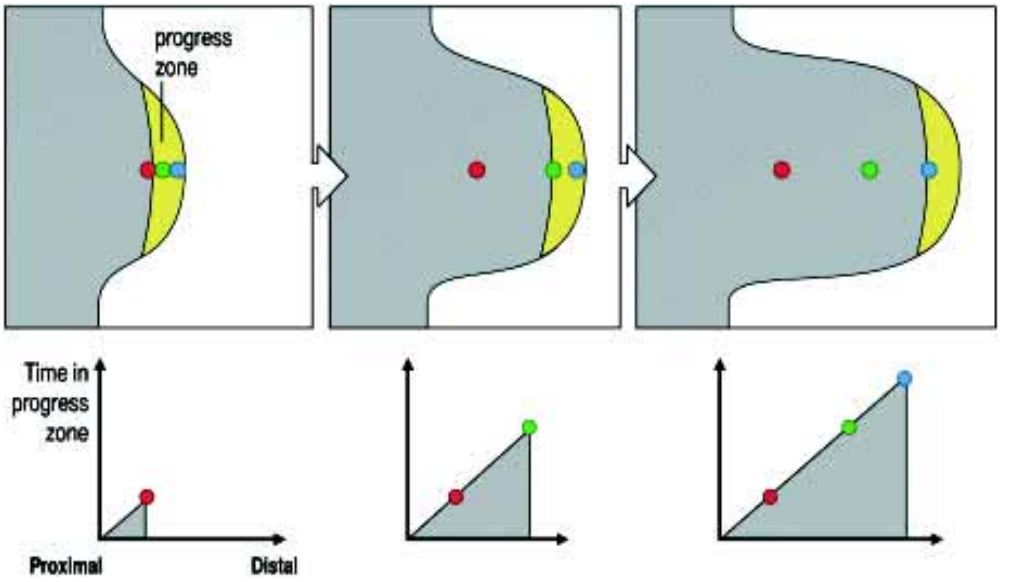

Fig. 1. A cell´s proximo-distal positional value may depend on the time it spends in the Progress Zone. *Cells continually leave the zone at the tip of the limb under the apical ectodermal ridge. Cells that leave early form proximal structures while cells that leave last form the tips of the digits.*

specification of the Hox genes along the antero-posterior axis of the embryo, the cells measuring the time they spend in the region linked to the regressing node.

A recent report by Tabin's group has questioned the validity of the progress zone. But there is, at present, no reason to accept, as has been suggested, that the progress zone has fallen victim to progress as the whole limb is specified very early in the bud, and in fact it still provides the only plausible model for proximo-distal patterning. The resolution of these issues in favour of early specification would come about if molecular differences corresponding to the proximo-distal elements were identified in the early bud. By contrast, if evidence for a timer such as an oscillator was found in/ at the tip of the bud, the progress zone model would be strongly supported . Time will tell. But rather like the letter from Mark Twain that the report of his death was an exaggeration, so it is with the progress zone.

References

DALE, K.A. and POURQUIE, O. (2000). *BioEssays* 22: 72-83.

DUDLEY, A.T., ROS, M.A. and TABIN , C.T. (2002). A re-examination of proximodistal patterning during vertebrate limb development . *Nature* 418: 539-544.

KERSZBERG, M. and WOLPERT, L. (2000). A clock and trail model for somite fromation,specialization and polarization. *J. Theoret. Biol.* 205: 505-510.

LEWIS, J. (1975). Fate maps and the pattern of cell division: a calculation for the chick wing bud. *J. Embryol. Exp. Morph.* 33: 419-434.

SUMMERBELL, D., LEWIS, J. and WOLPERT, L. (1973). Positional information in chick limb morphogenesis. *Nature* 244: 492-496.

TICKLE,C. and WOLPERT,L. (2002). Progress zone, alive or dead? *Nature Cell Biol.* 4E: 216 -218.

VARGESSON, N. *et.al.* (1997). Cell fate in the chick limb bud and the relationship to gene expression. *Development* 124: 1909-1918.

WOLPERT, L.,TICKLE, C. and SAMPFORD,M. (Appendix by J. Lewis) (1979). The efect of cell killing on pattern formation in the chick limb bud *J. Embryol. Exp. Morph.* 50: 175-198.