Parallel Progression Model of Metastasis

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In the 1950s, the parallel progression model of metastasis was developed as an alternative to the linear progression model. Whereas the linear progression model describes metastasis occurring as a result of a series of steps that take place sequentially, the parallel progression model assumes that the growth rates associated with metastasis are too large to have been initiated late in the development of primary tumors. Though the parallel progression model does not differ from the linear progression model in its suggestion of the general mechanisms mediating cancer growth, it does allow for metastasis to be initiated further from the primary tumor than does the linear progression model. Though there is some support for the linear progression model of metastasis, there is significant research to suggest that the parallel progression provides a superior model for the nature of metastatic growth.

Tumor and metastatic growth rate are, in certain ways, difficult to reconcile with the linear progression model. For example, the linear progression model requires a primary tumor and, as metastasis is the final stage of the linear progression model, it would be expected to occur much later in time than the development of the primary tumor. However, metastasis is sometimes diagnosed in early-stage cancer and also presents without a known primary tumor site 5-10% of the time in United States and European diagnoses. Though these circumstances appear to better support the parallel progression model, an important question is why, if growth and metastasis progress in parallel manner, there exists a correlation between the size of the primary tumor and the time and frequency of metastasis. A related question is why surgery on early tumors improve survival to a greater extent than does surgery on later stage tumors. One possible explanation that is not inconsistent with the parallel progression model is that as the primary tumor grows, it becomes increasingly capable of providing signals that enhance secondary tumor growth, thereby contributing to such growth without requiring linear progression. Such signals could involve cytokine and growth factor secretion.

The differences in genetic changes observed in primary tumors and metastasis appear inconsistent with the linear progression model. Though it may be argued that similarities in genetic changes in these populations support the linear progression model, similarities including the microenvironment of primary tumors and metastasis may lead to convergent evolution of distinct tumors rather than the derivation of tumors from other, similar tumors. Further, observations of disseminating tumor cells exhibiting genetic heterogeneity before the presence of metastasis conflicts with the linear progression model. Thus, the parallel progression model and comparable genetic alterations in distinct tumors are not mutually exclusive.

The linear progression model predicts that, in the case of multiple metastases, a new metastatic tumor emerges from a metastatic primary tumor. The parallel progression model, on the other hand, predicts that independent metastasis grow simultaneously. In previous decades, it was thought that attacking the initial metastasis may prevent further metastasis. However, research on the emergence of multiple metastases provides some insight into the low level of success associated with this oncological strategy. Specifically, there is little difference in the average time it takes for a primary tumor to produce a single metastasis versus multiple metastases.

If metastasis occurs in a manner more consistent with the parallel progression model than with the linear progression model, as much research suggests, new therapeutic interventions must be considered. Specifically, treatments that are
effective for certain cancer cells are likely to be ineffective for other cells is metastases propagate independently. Further, the parallel progression model raises the possibility that early-stage disseminating tumor cells in bone marrow, or circulating tumor cells in the blood, may allow for earlier cancer detection and treatment than previously believed.

References


