

MILESTONE 13

Environmental awareness

Context is everything for cells and, in addition to the importance of finding an appropriate blood supply (see [Milestone 7](#)), tumorigenic potential will often only be realized when cells find themselves in a tissue environment that they can subvert to their advantage. This phenomenon was first clearly noted in the 1970s, although it was decades before the cellular basis was uncovered.

In 1975, Beatrice Mintz and Karl Illmensee asked what would happen if mouse tetracarcinoma cells were placed in a 'normal' environment. They took the tetracarcinoma cells from embryoid bodies *in vivo*, and injected them into developing mouse blastocysts. Surprisingly, normal mice were born with no evidence of tumours. When the authors looked more closely, they found that tumour-derived cells were present in large numbers and contributed to several unrelated tissues, the most notable being functional spermatozoa. From this, Mintz and Illmensee concluded that the tumour cells were developmentally totipotent and could revert to normal behaviour in the appropriate environment. At the time, they also speculated that the original tumorigenic state might not involve a mutation.

This study was to have a strong influence on Mina Bissell. Inspired by this mysterious behaviour of tumour cells, Bissell began to focus her own research on the influence of the microenvironment. In 1984, she published a study, together with David Dolberg, showing that the ability of Rous sarcoma virus (RSV) to induce tumours was also context dependent. The tumour-inducing behaviour of RSV

when injected into the wings of newly hatched chicks was already known, and the viral gene *v-src* had been identified as the sole culprit.

What Bissell found, however, was that if RSV was injected into 4-day-old embryos, no tumours were produced, despite the spread of RSV infection throughout the embryo and active v-Src expression. Furthermore, if the infected embryonic cells were isolated and grown in culture, they now became transformed. So, something about the environment of the embryos was able to block tumorigenesis, despite the presence of v-Src. The following year, her group went on to show that wounding was one important influence on the ability of a cell to succumb to tumorigenesis. When RSV was injected into a chick wing to produce a local tumour, a second tumour would only be seen if a wound was simultaneously induced at a remote site. The Bissell group later found that the factor responsible was transforming growth factor- β (TGF- β) — an early and surprising demonstration of the dual action of this cytokine.

It is only during the past 10 years that we have begun to understand the molecular basis for how the local tissue environment, and processes such as inflammation and infection, can influence tumorigenic cells. For example, in 1997, Bissell and colleagues showed that blocking integrin function was sufficient to revert the malignant phenotype of human **breast cancer** cells both in culture and *in vivo*. Others, including the groups of Luis Parada and Harold Moses, were able to show in mouse models that genetic alterations in cells of the tumour microenvironment contribute to, and can even be sufficient for initiating, the development of cancer.

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References and links

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“These experiments form the groundwork for our current understanding that the environment in which cells are growing can influence the expression of the transformed phenotype” Sara Courtneidge

URLs

v-src

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=1491925

breast cancer

<http://www.cancer.gov/cancertopics/types/breast>