THE TWO FACES OF METASTASIS

During development, the cells of an embryo change their pattern of gene expression, which allows them to detach from their original location and migrate to another part of the embryo, where the pattern changes again to allow formation of a new organ. Cancer stem cells (CSCs) may behave in a similar way, changing their gene expression to either grow rapidly and generate the tumor mass, or stop growing and traverse the bloodstream unharmed by its shearing forces. This new idea may help explain conflicting observations in the field.

TUMOR 1
CSCs had been identified by their CD44 markers and the expression of a developmental program called the epithelial-to-mesenchymal transition (EMT). They were thought to generate additional CSCs as well as non-self-renewing bulk tumor cells. These EMT CSCs were associated with more aggressive tumors, but newer research suggested that they are also quiescent, or unable to replicate in number, creating confusion in the field.

However, recent findings suggest that CSCs can exist in two different states: the EMT, which expresses CD44 and can not replicate easily, and a converse transition state called the mesenchymal-to-epithelial (MET), in which cells express aldehyde dehydrogenase (ALDH), and replicate rapidly. The stationary MET cells spawn tumor cells, but do not metastasize unless they receive signals, such as transforming growth factor beta (TGFB), IL-6, and hypoxia, which cause them to convert into EMTs. The EMT cells then release their epithelial anchors (integrins) to the extracellular matrix and enter the bloodstream to travel to distant locations in the body.

TUMOR 2
Once the EMT cells settle into a new location they remain dormant without the ability to replicate, until new signals instigate their conversion to the rapidly growing MET CSCs. These signals include bone morphogenic protein (BMP) and HER2. MET cells can be differentiated from their EMT counterparts via the expression of aldehyde dehydrogenase (ALDH).