Identification and characterization of mechanisms underlying collective cell migration

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Abstract

The process of cell migration is critical for diverse physiological and pathological processes, including embryonic development, immune surveillance and cancer metastasis. Cell migration at the single-cell level has been studied extensively over many decades, and is known to proceed via repeated cycles of lamellipodial protrusion, formation of new matrix adhesions at the cell leading edge, and retraction at the rear of the cell. The rate and directionality of single-cell migration are determined by the length, frequency and angular persistence of the migratory cycles, and believed to be regulated by Rho and Rac GTPase. Collective cell migration is another mode of cell locomotion, particularly prevalent during embryogenesis and organogenesis, where it drives the formation of the germ layers during gastrulation, as well as the assembly of complex tissues and organs. This type of migration is also prevalent in many invasive and metastatic tumors. During collective migration, the cells remain physically connected, and the integrity of cell-cell junctions is largely preserved. Multicellular polarity and organization of the actin cytoskeleton generate traction and protrusive forces that drive the migratory process, and determine its directionality. In most modes of collective cell migration, the underlying extracellular matrix (ECM) along the migratory path is remodeled either mechanically or enzymatically.

In the past, many of these migratory features were studied phenomenologically, and thus the molecular basis for the coordinated migration of multiple cells, primarily in invasive cancers, is still poorly understood. In order to explore the mechanisms underlying collective cell migration, we are searching for novel genes involved in this process in breast carcinoma cells, using an siRNA screening approach. Genes found to affect collective cell migration are being tested for their involvement in various types of cancer cells, and will be subjected to further in-depth analysis, to determine their mechanism of action. We believe that this project will provide new insights into the mechanisms involved in cell-cell communication during migration, and may identify new therapeutic targets associated with cancer cell invasion.