

Cancer cells: Some types control continued tumor growth, others prepare the way for metastasis

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A study from Massachusetts General Hospital (MGH) researchers suggests that specific populations of tumor cells have different roles in the process by which tumors make new copies of themselves and grow. In their report in the May 15 issue of *Cancer Cell*, researchers identify a tumor-propagating cell required for the growth of a pediatric muscle tumor in a zebrafish model and also show that another, more-differentiated tumor cell must first travel to sites of new tumor growth to prepare an environment that supports metastatic growth.

"Most investigators have thought that tumor-propagating [cells](#) – what are sometimes called cancer stem cells – must be the first colonizing cells that travel from the primary tumor to start the process of local invasion and metastasis, but in this model, this is simply not the case," says David Langenau, PhD, of the MGH Department of Pathology and Center for Cancer Research, who led the study. "Instead, the colonizing cells lack the ability to divide and instead prime newly infiltrated regions for the eventual recruitment of slow-moving cancer stem cells. It will be important to test how broadly this phenomenon is found in a diversity of animal and human cancers."

Langenau's team has long been using zebrafish to study rhabdomyosarcoma (RMS), an aggressive pediatric cancer. In embryonic zebrafish, RMS can develop within 10 days, and since the tiny fish are transparent at that stage, fluorescent markers attached to particular

cellular proteins can easily be imaged. The current study used these properties to monitor how specific populations of [tumor cells](#) develop and their role in initiating new [tumor growth](#).

Previous research from the MGH team had discovered that RMS cells expressing marker proteins also seen on muscle progenitor cells had significantly more tumor-propagating potential than did other tumor cells. Fluorescently labeling proteins associated with different stages of cellular differentiation revealed distinct populations of RMS cells in the zebrafish model. Cells expressing the progenitor cell marker *myf5*, were labeled green, and those expressing myogenin, a marker of mature muscle cells, were labeled red.

In a series of experiments, the research team confirmed that *myf5*-expressing RMS cells had powerful tumor-propagating potential, but the ability to visualize how tumor cells move in living fish produced a surprising observation. While *myf5*-expressing cells largely remained within the primary tumor itself, myogenin-expressing RMS cells easily moved out from the tumor, entering the vascular system and passing through usually impenetrable layers of collagen. Only after the more-differentiated but non-proliferative myogenin-expressing cells had colonized an area did the *myf5*-expressing tumor-propagating cells appear and start the growth a new tumor. Imaging the labeled tumor cells also revealed that different cellular populations tended to cluster in different areas of later-stage tumors.

"Our direct in-vivo imaging studies are the first to suggest such diverse cellular functions in solid tumors, based on differentiation and the propensity for self-renewal," says Myron Ignatius, PhD, of MGH Pathology and Center for Cancer Research, the study's first author. "I think we will find that this kind of division of labor is a common theme in cancer, especially given that the vast majority of cells within a [tumor](#) are not tumor-propagating cells. We suspect there will be molecularly

defined populations that make niches for tumor-propagating cells, secrete factors to recruit vasculature and create boundaries to suppress immune cell invasion."

Langenau adds, "Division of labor is a new and emerging concept in [cancer](#) research that we hope will lead to new targets for rationally designed therapies. In rhabdomyosarcoma it will be important to target both the tumor-propagating cells and the highly migratory colonizing cells for destruction – a major focus of ongoing studies in our group." Langenau is an assistant professor of Genetics at Harvard Medical School and a principal faculty member at the Harvard Stem Cell Institute.

Provided by Massachusetts General Hospital

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