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Title of Research: Discovery of Unique 3D Behaviors in Human Melanoma: New Targets for Anti-Cancer Drug Treatments

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Introduction/Purpose:

We developed a high-resolution 3D motion analysis system to reconstruct, motion analyze and test drug responses of tumors formed in a model tumor 3D culture system. Application of this 3D tumorigenesis model to tumor explants from cancer patients led to the discovery of unique behaviors in cancer cells that are not observed in normal cell preparations including high levels of single cell motility through a dense fibrous matrix and aggregate (model tumor) formation. We also identified specialized cell types that facilitate model tumor formation. We have documented these behaviors in many different cancers including breast, paraganglioma, lung, peritoneal fluid, brain and now melanoma (skin cancer). In addition, initial experiments with fresh melanoma preparations revealed behaviors not observed in other tumors. These include extremely high single cell velocities and fusion of aggregates via tunneling of a highly aggressive subpopulation of cells through the dense matrix. If these differences hold true for other aggressive melanoma cells, then very different targets may have to be considered for melanoma drug development than those targeted for other cancers. We are now analyzing additional melanoma tissue as well as the ability of anti-cancer drugs to inhibit the unique melanoma behaviors.

Experimental Design:

Cells are embedded in a 3 dimensional matrix called matrigel. These three dimensional cell cultures are recorded using a unique three dimensional recording system. Images from the recording system were reconstructed and analyzed using jDIAS, a unique motion analysis program developed in the Soll laboratory.

Results:

As time progresses, non-tumorigenic cells divide and form cell islands, but do not coalesce to form larger sub-tumors. In melanoma patient samples, aggregates coalesce to form larger model tumors. As time progresses, tumorigenic aggregates coalesce. In melanoma patient samples, aggregates coalesce to form larger model tumors. In melanoma patient samples, initial aggregates coalesce using filopodia. . A newly discovered cell, not involved in coalescence called the dervish cell moves rapidly through the matrix. In melanoma patient samples, pioneer cells dig tunnels through the extracellular matrix. These tunnels are used by other cells to move through the matrix

Conclusions:

We have identified behaviors unique to model tumor formation in melanoma preparation which, if proven to be present in vivo, could provide targets for new anti-cancer drugs. The system we have developed at the University of Iowa is unique and should serve as a model for other scientists screening for new drugs.