Instituto de Medicina Molecular João Lobo Antunes

Master Project Proposal

Title: Mechanisms of nuclear positioning during metastasis

Synopsis:

Position of the nucleus is important for cellular activities such as cell division, cell migration and multicellular organism development. The cytoskeleton plays an important role in nuclear positioning either by anchoring or moving the nucleus within the cell.

In our lab we are interested in understanding how does the cytoskeleton regulates nuclear positioning and what is the role of nuclear positioning during cell migration in metastatic cells (1,2,3).

Cell migration is required for efficient metastasis of tumors. We recently found that migrating cells move their nuclei away from the front of the cell prior to migration by physically connecting the nucleus to the actin cytoskeleton (1,2). In addition, we also found that inhibition of nuclear positioning blocks cell migration.

We performed a siRNA screen against predicted nuclear envelope protein and identified several molecules required for nuclear movement and cell migration (4). We propose to study how these proteins are involved in the physical connection between the nucleus and the actin cytoskeleton during cell migration (see Fig1 and Fig2 below). We use state-of-the-art microscopy techniques (multicolor time-lapse fluorescent microscopy, photo-activation and photo-switchable techniques, fluorescence recovery after photobleaching - FRAP) combined with molecular biology, biochemistry and micromanipulation (microinjection) approaches to address this process both in vitro and in vivo. The mechanisms of nuclear positioning during cell migration that we will identify are potential targets for therapies to inhibit abnormal cell migration that occur during cancer metastasis.

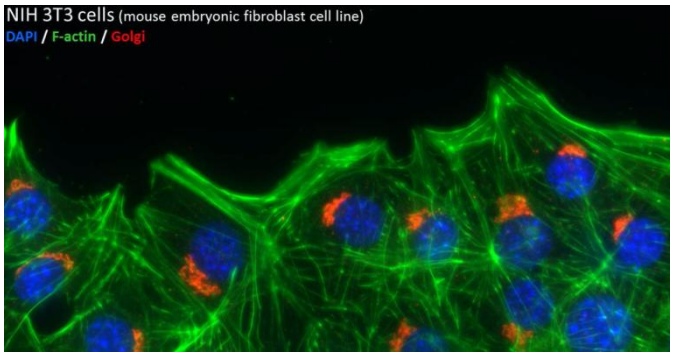

Figure 1 – NIH 3T3 cells fixed after wound assay. Immunofluorescence was done to label the nucleus using DAPI (in blue), F-actin using phalloidin (in green) and Golgi using a set of primary and secondary antibodies (in red). Notice the majority of the nucleus are positioned towards the rear of the cells.

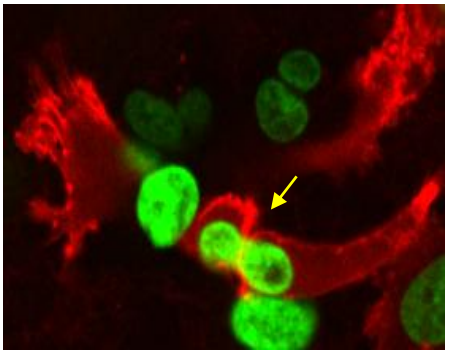

Figure 2 - Live tumour cell migrating in a 3D environment mimicking a tumour metastasis. Notice how the nucleus (green) is squeezed by actin (red) during this process (yellow arrow).

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Remunerated or volunteer training: Volunteer