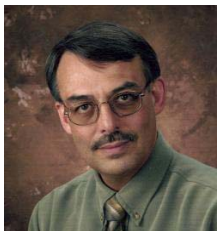

GAP JUNCTIONS, TUMOR SUPPRESSION & METASTASIS

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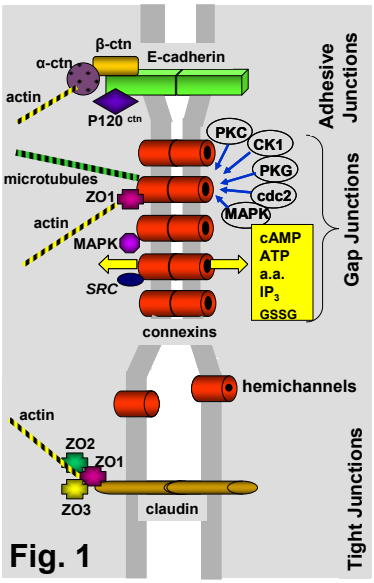

Fig. 1

Gap junctions, comprised of a diverse family of proteins called connexins (Cx), are a part of the complex junctional systems between cells that mediate the direct exchange of signaling molecules and other metabolites between cells through channels that connect adjacent cells **(Fig. 1)**. Connexins have been identified as tumor suppressors in several human screens of breast and prostate cancer, and their expression in transformed cells has often been associated with reversal of the transformed phenotype. However, the underlying molecular mechanisms have remained elusive because of our limited understanding of the critical molecules that pass through these channels.

Using the HeLa cervical cancer cell line as a model, we have demonstrated that Cx26, the endogenous connexin of the cervix, and not two other connexins, can reverse the transformed phenotype of HeLa cells, making them dependent on serum and anchorage to substrate for growth. Using various mutants of Cx26 that selectively ablate hemichannel and gap junction functions, we can demonstrate that this growth suppression requires intercellular exchange of metabolites that lead to partial block of the cell cycle. Analysis of signaling pathways that regulate the cell cycle has implicated a redistribution of cAMP between cells, and subsequent activation of PKA, as critical in this process. As cAMP levels are known to oscillate during the cell cycle, this represent a previously unstudied mode of regulating growth through the spatial distribution of exisiting signals, rather than de novo synthesis of new signaling molecules **(Fig. 2)**. In parallel with these growth studies, our lab is also investigating the selective enhancement of motility in these cells that is mediated by Cx26 coupling, and how coupling can regulate cell adhesiveness and metastatic potential

In order to correlate the selective effects of different connexins on cell growth, we have also been measuring the differential permeability of different connexin gap junctions to natural permeants. The lability and low abundance of metabolites makes this a challenging task, and we are the only lab to obtain these measurements, which have shown that different connexin channels can show remarkable selectivity, distinguishing between AMP and cAMP, differing by a single phosphate bond.

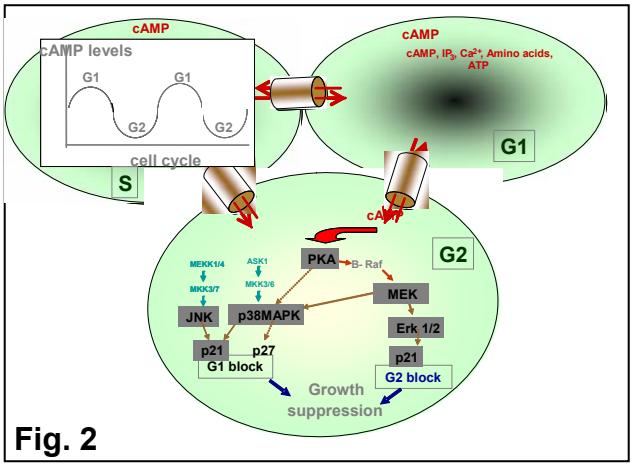

Fig. 2

Using mutagenesis, electrophysiology and chemical modification, we have mapped which residues line the pore in different connexins, and are now attempting to determine for the first time how such large pores distinguish between permeants. Thus, through the combined application of imaging, analysis of signal transduction pathways, and structure function studies, we are developing a comprehensive understanding of the long standing puzzle of why communication between tumor cells through gap junctions can suppress growth, while also enhancing metastatic potential. These mechanisms will be critical to devising rational strategies to treatment of many cancers.