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CELL SIGNALING DOWNSTREAM OF CELL-CELL CONTACT

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During the organization of tissue structures cells must communicate with the contacting cells. However, it remains elusive how cell-cell contact information is converted to intracellular signals. We found that cells in contact with neighbouring cells generate local transient increases in the intracellular Ca^{2+} concentration. The Ca^{2+} transient was dubbed 'Ca^{2+} lightning' because it appeared like lightning seen through a thundercloud when it was imaged using total internal reflection fluorescence microscopy. Ca^{2+} lightning was observed near cell-cell contact regions and was hardly observed in the central regions of cells, nor was it found in solitary cells that are not in contact with other cells. We also found that Ca^{2+} lightning is capable of regulating cell-cell repulsion via PYK2, a Ca^{2+}-activated protein tyrosine kinase, which induces focal adhesion disassembly in a Ca^{2+}-dependent manner. These results indicate that cell-cell contact information may be transmitted by Ca^{2+} lightning to regulate intracellular events.

Key Words: Calcium, cell-cell repulsion, PYK2, imaging

S 14-3

G-PROTEIN-COUPLED RECEPTOR SIGNALING NETWORKS

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G protein-coupled receptors (GPCRs) constitute the largest family of cell surface molecules involved in signal transmission. These receptors are involved in many physiological functions, and they aberrant activity can result in a number of disease states, including cancer. Emerging evidence suggests that GPCR-initiated signaling pathways also play a central role in viral infection, immune evasion, and viral tumorigenesis. Fore example, the Kaposi's sarcoma (KS) associated herpesvirus (KSHV), the infectious cause of KS, the most common neoplasm arising in AIDS patients, expresses an open reading frame encoding a constitutively active GPCR, *vPCR*. Surprisingly, while using a recently developed high throughput *in vivo* endothelial specific retroviral gene transfer system to express candidate KSHV oncogenes in mice, we observed that among the many KSHV genes tested only *vPCR* was able to promote the development of visible vascular tumors that strikingly resembled human KS lesions. Furthermore, we observed that *vPCR* can transform endothelial cells as well as promote the tumoral growth of cells expressing KSHV latent genes in a paracrine fashion. Thus, *vPCR* may play a critical role in initiating KS tumor development, and can also unmask the sarcomagenic potential of KSHV latent genes. Ongoing studies using high-throughput animal models to study the molecular mechanisms underlying the transforming activity of *vPCR* through the stimulation of heterotrimeric G proteins, MAP kinase signaling networks, small GTPases of the Rho family, and the PI3K-Akt-mTOR pathway will be presented. Ultimately, this knowledge may contribute to the identification of novel molecular targeted therapies to treat KS and other diseases that involve aberrant endothelial cell function, including tumor induced angiogenesis.