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Getting to the Heart of Cell Signaling

Researchers have discovered new details about how one of the cell's most commonly used messenger molecules, cyclic AMP, can trigger several distinct responses within cells. The studies point the way toward new drug targets for heart disease and other disorders.

John D. Scott, a Howard Hughes Medical Institute investigator at Oregon Health and Science University, and his colleagues published their findings in an article in the September 22, 2005, issue of the journal *Nature*.

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— John D. Scott

Cyclic AMP (cAMP) is a cellular chemical that, among other things, can control heart rate and muscle contraction. Cyclic AMP also regulates the passage of calcium through ion channels in the cell membrane, another important cellular process in the heart.

A major question, said Scott, has been how the cell organizes multiple cAMP signals in space and time within the cell. "You can have two hormones that activate the same cell using the same chemical, cyclic AMP, to generate distinct physiological responses. One of the insights that has come from our past work is a potential explanation for that ability — that these hormones do not activate cyclic AMP globally in the cell, but rather cyclic AMP accumulates in distinct regions of the cell."

In their new study, Scott and his colleagues explored a group of proteins called muscle-specific A-kinase anchoring protein (mAKAP) complex, which acts as a sort of central molecular clearing house for cyclic AMP signals. Previous studies had indicated that AKAP complexes only bind one cAMP target, which is protein kinase A (PKA), said Scott. However, in an earlier study, first author Kimberly Dodge-Kafka had found that mAKAP also binds phosphodiesterase, which is also an important protein in regulating cAMP signaling.

"Kim's finding enabled us to think of a scenario in which cyclic AMP could work at a particular location and time in the cell," said Scott.

To investigate that possibility, the researchers sought to illuminate the signal transduction process by using reporter molecules that carry specific fluorescent dyes. These reporters can substitute for the normal targets of PKA action. By observing how the fluorescence is transferred from one protein to another — a phenomenon called fluorescence resonance energy transfer (FRET) — the researchers can determine the activity of PKA and associated molecules.

These studies, combined with biochemical studies, revealed important details of how PKA, phosphodiesterase, and a third signaling molecule — called exchange protein directly activated by cAMP 1 (Epac1) — regulate cAMP signaling, said Scott. "This showed that cAMP could work in a manner that didn't always involve protein kinase A," Scott said. "These findings also reveal how the cyclic AMP regulatory system has three spatial dimensions and a fourth dimension — time — that give the system a great degree of specificity within the cell. It allows a real segregation of signals because they are separated by both space and time."

The researchers also showed that manipulating the mAKAP complex with drugs induced excessive growth, or hypertrophy, of the cultured cardiac cells they studied. "The hypertrophy we saw is a good model for the changes in structure and regulation of cardiac cells under stress seen in certain kinds of heart disease," said Scott. "There is important clinical relevance to these findings, because heart disease is the number one killer in people over age eighty-five in this country."

Scott said their findings suggest that new treatments for heart disease could target phosphodiesterase to influence cyclic AMP signaling, since "changes in the cyclic AMP pathway are known to be linked to heart disease, and heart contraction is linked to calcium and cAMP signaling."