The Oncologist
Physician Education

The Molecular Perspective: The *ras* Oncogene

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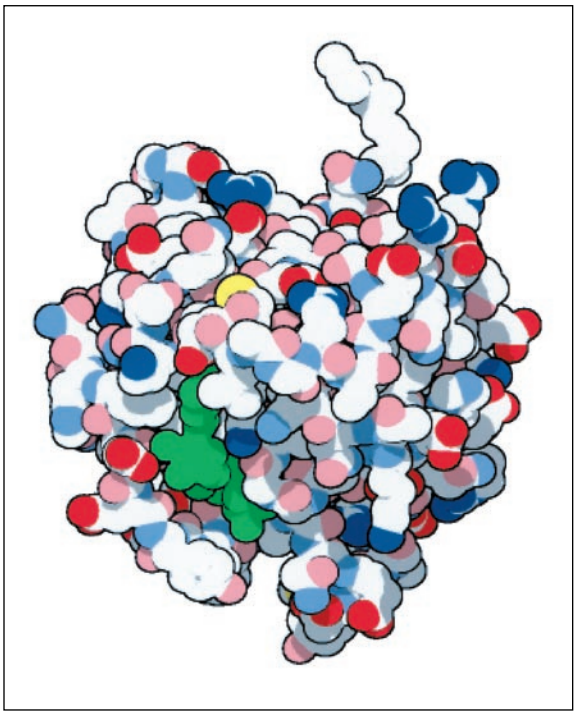

Figure 1. Ras protein. *Ras is a small protein with a central function. In this illustration, carbon atoms are in white, oxygen is in red (for charged atoms) and pink (for uncharged atoms), nitrogen is in shades of blue (bright blue for charged atoms), and sulfur is yellow. Hydrogen atoms, which are not seen in the crystallographic structure, are not shown. Two features are readily apparent. At the top, the lipid-like farnesyl group extends upward, ready to attach the protein to the cell membrane. At bottom left, the guanine nucleotide, in green, is bound in a deep cleft. Oncogenic mutations typically change amino acids in the protein loops surrounding the nucleotide, uncoupling the state of the nucleotide from any change of conformation in the protein. Coordinates were taken from entry 121p in the Protein Data Bank.*

Cells continually gossip with their neighbors, deciding together when to divide, when to differentiate, and when to die. Often, cells communicate with one another by delivering protein messages. These proteins—hormones, growth factors, chemokines, etc.—are far too large to enter the receiving cell, so an elaborate mechanism of signal transduction has been developed, to transmit messages from the cell surface into the cell nucleus, where the topic of conversation is implemented as a change in gene expression.

As one might imagine, mutation of proteins within these signal transduction pathways has disastrous consequences. If the message is altered, the cell may get a false message to proliferate, leading to cancer. For this reason, the genes of many signal transduction proteins were first discovered in their role as *oncogenes*—genes that lead to cell transformation when mutated—before their functions in normal cells were elucidated.

The *ras* oncogenes were among the first to be discovered. The Ras proteins deliver signals from cell surface receptors, such as growth factor receptors, G-protein coupled receptors that recognize molecules such as thrombin and bradykinin, and integrins. These signals are then passed protein-to-protein along several different pathways, ultimately effecting mitogenic functions such as lipid metabolism, DNA synthesis, and cytoskeletal organization. Disruption of these signals through mutation of the *ras* gene is involved in many tumor types, including roughly half of all colon cancers and 90% of pancreatic carcinomas.

The Ras protein sits at the center of a many-tiered cascade of molecular interactions. Most of the proteins along this cascade are activated by phosphorylation, but Ras uses a bound guanine nucleotide to toggle between its “on” and “off” states. Normally, Ras binds GDP in its neutral state. A message is

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Figure 2: A Ras signaling pathway. *The mitogenic signal delivered by platelet-derived and epidermal growth factors activate the Ras signaling pathway. A complex series of interactions carry and amplify the signal from the cell-surface receptor to the nucleus. The signal begins at the top of the illustration. The cell membrane runs horizontally, and growth factor (yellow) has brought two receptor molecules (yellow-orange) together. These receptors span the membrane, and when brought adjacent, the portions on the interior side of the membrane phosphorylate themselves. These phosphorylated receptors are then recognized by adapter molecules, such as Grb2 and Shc (orange), which use SH2 domains to recognize the phosphorylated site. These adapters then bind to the guanine nucleotide exchange factor SOS (named after the Drosophila gene* son-of-seven-less*). This protein then interacts with Ras (red), expelling the GDP nucleotide and allowing GTP (green) to bind. Ras then triggers a cascade of MAP kinases, shown ranging from light pink to dark pink, that deliver the signal to its target. Other molecules seen in the illustration include long, sinuous spectrin proteins just under the cell membrane, and sturdy actin filaments crisscrossed through the cytoplasm below.*

passed from the receptor to Ras by guanine nucleotide exchange factors (GEFs) that expel this GDP, allowing GTP, which is more plentiful in the cytoplasm, to bind in its place. GTP causes a subtle rearrangement of the protein, which then triggers a cascade of mitogen-activated protein kinases. These kinases ultimately phosphorylate the target, such as a transcription factor, delivering the message to its final destination.

This signal is necessarily self-limiting. Ras hydrolyzes GTP to GDP fairly quickly, turning itself "off," and a collection of GTPase-activating proteins (GAPs) speed up the process, ensuring that the amount of active Ras within the cell is tightly linked to the amount of receptor that is bound at the cell surface. Imagine, however, what happens when Ras loses this control. Oncogenic mutation makes Ras insensitive to the state of the nucleotide, so it is continually switched "on." The message is delivered continuously, giving the cell unchecked permission to proliferate.

There is some hope for treatment of cancers that show mutations in the *ras* oncogene. The early steps of signal transduction, from receptor to Ras, occur on the inside of the cell membrane. Ras itself is tethered to the membrane through a short isoprenoid group, which is attached to a specific cysteine on the protein soon after it is synthesized. The modification is performed by the enzyme farnesyltransferase. Inhibitors of this enzyme block the maturation of Ras, and thus are promising candidates for targeting of rogue cells with *ras* oncogenes.

Additional Reading:

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