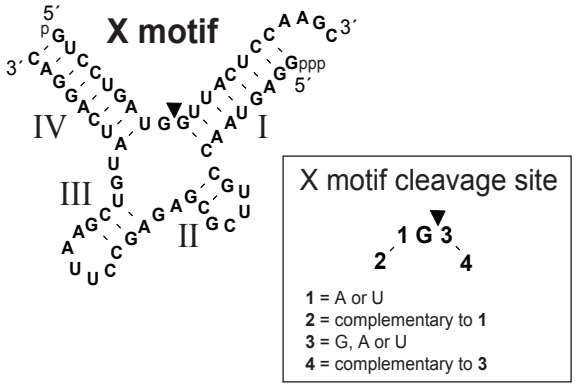
Breaker Laboratory

Molecule of the Year 2001

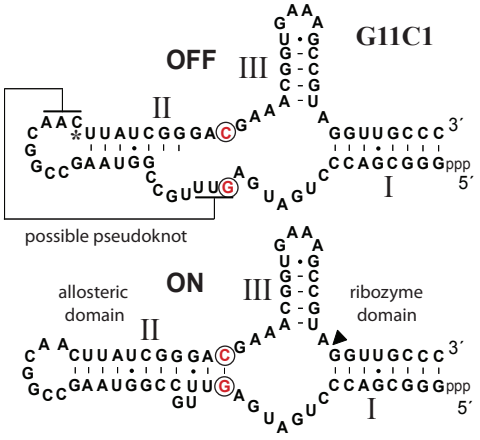
X-motif

Fig. 1. Sequence and secondary structure of the X-motif. Arrowhead indicates the site of RNA transesterification and the roman numerals identify four stem elements that are necessary for catalytic action. Substrate specificity is defined by base pairing within stems I and IV, wherein the nucleotides at the cleavage site follow the rules as given in the box.



Proton Sensors and "Molecular Memory"

Fig. 2. Sequence and secondary structure model of a proton-sensitive ribozyme. Ribozyme G11C1 exhibits hammerhead self-cleavage activity only when pulsed with acid (pKa ~4.6). The allosteric transition appears to require a critical C residue (asterisk) for proton-dependent activation.



In recognition of the X-motif's sophisticated active site and in recognition of the complex molecular switch function of RNA with proton-sensing/molecular memory activities, the status of Breaker Laboratory "Molecule of the Year" has been jointly conferred upon these two molecules.

Catalytic action by RNA is believed to be limited by the chemical strategies that are employed by the active site of a given ribozyme. The X-motif appears to have a superior active site that simultaneously uses at least three strategies: in-line attack; metalation of a non-bridging phosphate oxygen, and metalation of the 5' bridging phosphate oxygen. If optimized, the X-motif would be capable of operating as fast as protein enzymes that catalyze the same phosphoester transfer reaction. Sophisticated functions are also exhibited by a proton-sensitive ribozyme that was isolated as a selfish molecule from an in vitro selection reaction. The G11C1 ribozyme is activated by an acid pulse, and can retain its active conformation for many hours. This finding indicates that complex RNA switches could be made to serve in biotechnology and nanotechnology applications.

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