In the famous “PaJaMo” experiment, Arthur Pardee, Francois Jacob, and Jacques Monod exploited the technique of diploid analysis to show that a repressor controlled expression of the Lac operon. Loss-of-function (recessive) mutations in the lacI gene confer a constitutive phenotype (1). Subsequently (for a review, see reference 2), it was shown that lacI mutations that destroy the inducer binding site (superrepressor, $I^S$) confer a dominant, non-inducible phenotype and that the repressor turns off expression by binding a site, called the operator, that was defined by cis-dominant constitutive mutations ($O^C$). Because the repressor model was so elegantly simple and it offered satisfying explanations for regulatory systems as seemingly diverse as bacteriophage λ, negative control by a repressor soon became generally accepted as the universal model of gene regulation.

Ellis Englesberg was the first to challenge the universal nature of negative control with his studies of the arabinose operon. In a classic Journal of Bacteriology paper (3), Englesberg et al. used diploid analysis to show that araC mutations that confer a non-inducible phenotype cannot be $I^S$-like because they are recessive. This result suggests that the product of the araC gene is needed to turn on the ara operon, and the authors coined the name “activator” to emphasize the role of this protein in positive control.

Englesberg et al. (3) also isolated constitutive mutations and showed that they were not $O^C$-like because they were not cis-dominant; they mapped to araC ($araC^C$) and could complement araC null mutations in trans. However, a complication emerged with the discovery that the $araC^C$ mutations were recessive to $araC^+$

This should not be the case for a regulatory protein that functioned in a purely positive fashion. To account for this complication, Englesberg et al. proposed an additional twist to the Lac model. In the absence of inducer, LacI binds the operator and represses expression; the inducer allosterically changes the conformation of LacI to an inactive form. Like LacI, AraC exists in two conformations. However, in contrast to LacI, both conformations of AraC are active; in the absence of inducer AraC acts as a repressor, and in the presence of inducer it acts as an activator to stimulate expression. The $araC^+$ mutation is recessive because repression is epistatic to activation.

The model presented in the Englesberg et al. paper (3) has withstood the test of time and is basically correct. However, partly because of the fact that AraC did function as a repressor and partly because of vociferous resistance to the concept of positive control from influential scientists such as Monod, it would take Englesberg several more years and the accumulation of overwhelming evidence that there was no LacI-like repressor in the Ara system before his model and the concept of activators were generally accepted. Ironically, activators turn out to be far more common in eukaryotes than repressors.

REFERENCES