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Milestone 6

One-way traffic

Cell division occurs by an ordered series of metabolic and morphogenic changes that are collectively termed the cell cycle. This cycle is divided into four distinct phases. Replication of the chromosome occurs in the S (synthetic) phase, whereas cell division itself takes place in the M (mitotic phase). The gap (G) between completion of the M phase and the beginning of the S phase is termed the G1 phase, and the period between the end of the S phase and beginning of the M phase is called the G2 phase. Control mechanisms operate both to regulate the onset of each phase and to avoid improper transitions between phases. Important clues to the nature of cell-cycle regulation were established by Rao and Johnson in their 1970 paper in *Nature*.

Rao and Johnson used inactivated Sendai virus to fuse together mammalian cells that had reached different stages of the cell cycle. The resulting heterokaryons possessed two different nuclei — one from each parent cell — and share the same cytoplasm. The behaviour of the two nuclei was then monitored using microscopy to measure the duration of M phase, and radiolabelling of newly synthesized DNA to follow S phase.

In the first set of experiments, S-phase cells were fused with G2-phase cells. Although chromosome replication continued in the S nucleus of the heterokaryon, the G2 nucleus was unable to synthesize DNA, indicating that the G2 nucleus is prevented from entering further rounds of DNA replication. Rao and Johnson also found that the S/G2 heterokaryons entered M phase earlier than did S/S cells, indicating that the G2 nucleus accelerates the progress of the S nucleus towards mitosis.

In the second set of experiments, fusion of S-phase cells with G1-phase cells led to the rapid induction of DNA synthesis in the G1 nuclei. These observations led to the hypothesis that S-phase cells contain factors that induce DNA synthesis, and that these factors can diffuse freely between the nucleus and cytoplasm.

Finally, Rao and Johnson observed that when G1 cells were fused with G2 cells, the rate of initiation of DNA synthesis and of mitosis was similar to that of G1/G1 cells rather than G2/G2 cells. In other words, whereas the G2 nucleus had no effect on the G1 nucleus, entry of the G2 nucleus into M phase was delayed by factors associated with the G1 component.

This elegant series of experiments was the first indication in mammalian cells that the sequential and unidirectional phases of the cell cycle are controlled by a series of chemical signals that can diffuse freely between the nucleus and cytoplasm. The identification of these factors at the biochemical level has been a principal focus of research ever since.

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ORIGINAL RESEARCH PAPER
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Cell cycle