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A clonal study of the reversible inhibition of muscle differentiation by the halogenated thymidine analog 5-bromodeoxyuridine ☆

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Abstract

The thymidine analog 5-bromodeoxyuridine (BUdR) is well known for its mutagenic effects when incorporated in DNA. Similarly, BUdR has been reported by several workers to inhibit cytodifferentiation when applied during the cell proliferative phase. We have observed that relatively low levels (ca $10^{-6}M$) of BUdR, IUdR, ClUdR, and BCdR all cause a gradual change in cell morphology, and inhibit the fusion of cells to form syncytia in muscle clones, but do not interfere with proliferation of mononuclear cells. The inhibition of differentiation can be reversed by further cell division in the absence of the analog. After several days, this results in clonal cultures which are indistinguishable from untreated controls both in terms of total number of clones and of the proportion of clones which are myogenic; thus the drugs are not acting either by cell selection or mutagenesis.

BUdR is incorporated into DNA in place of thymine, its effect on differentiation can be competitively prevented by simultaneous inclusion in the medium of TdR or compounds readily convertible to TdR, and it has no detectable effect on postmitotic cells (muscle fibers). Although this suggests that BUdR exerts its effect on differentiation from a site in the DNA, an effect on cell metabolism at some other level cannot be ruled out.

Abbreviations

RNase, ribonuclease; DNase, deoxyribonuclease; PTA, phosphotungstic acid; FUdR, 5-fluorodeoxyuridine; ClUdR, 5-chlorodeoxyuridine; BUdR, 5-bromodeoxyuridine; TdR, thymidine; BCdR, 5-bromodeoxycytidine; IUdR, 5-iododeoxyuridine; BUR, 5-bromouridine; BU, 5-bromouracil; OHMeUdR, 5-hydroxymethyldeoxyuridine; 2,6-DAPdR, 2,6-diaminopurine deoxyriboside; 5-MeCdR, 5-methyldeoxycytidine; T, thymine; CdR, deoxycytidine; UdR, deoxyuridine; UR, uridine; U, uracil; TR, thymine riboside; AdR, deoxyadenosine; 3-MeCdR, 3-methyldeoxycytidine

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