Commentary on Eagle and Foley: "Cytotoxicity in Human Cell Cultures"

Michael B. Sporn


From a contemporary perspective in 2016, it is difficult to realize that not very long ago, the prevailing primary screen for testing new anticancer drugs was the demonstration of their therapeutic activity in vivo in animal models. Such assays were performed in mice that had been previously transplanted with highly malignant allogeneic or isogeneic carcinomas, leukemias, or sarcomas, which resulted in the subsequent death of the host mice if they were left untreated. The ability of a new drug to extend time to death was used as an endpoint of desired therapeutic activity.

Although these in vivo assays were cumbersome and expensive, and also required relatively large amounts of any new drug (as it was necessary to treat the mice repeatedly over many days), they were widely used and yielded results of major significance in cancer research performed in the 1940s and 1950s. Thus, the groundbreaking investigations by Hitchings and Elion on the synthesis of new purine analogues, which led to the eventual clinical use of 6-mercaptopurine as a component of life-saving leukemia therapy, relied on in vivo testing of newly synthesized purine analogues to evaluate their potential value as new drugs (1).

However, as efforts to synthesize new anticancer drugs increased markedly in the 1950s, it became apparent that a more efficient and less costly primary screen of new compounds was critically needed. The publication of Eagle and Foley’s article in Cancer Research (2) in 1958 thus was of major importance as a definitive statement of the utility of cell culture technology for evaluating new drugs. In this landmark article, 180 compounds, which had previously been tested in vivo for therapeutic activity against at least three transplanted tumors, were systematically evaluated for cytotoxicity in two human cell cultures derived from either malignant or normal tissues. The human cells used were the malignant KB line, derived by Eagle from an epidermoid carcinoma of the nasopharynx (3), and a nonmalignant cell strain from normal liver, recently established by Chang (4). The known anticancer activity in vivo of the 180 compounds ranged from highly active to essentially inactive.

The results reported in Eagle and Foley’s cell culture studies showed that the compounds that had been known to be active in vivo were also highly cytotoxic to both KB cells and Chang liver cells in culture. Cytotoxicity was essentially equivalent in both KB and Chang liver cells. Furthermore, compounds that were inactive drugs in vivo were largely inactive in cell culture; false positives were relatively rare, as only 19 of 91 (21%) compounds, inactive in vivo, were found to be cytotoxic to the cell cultures.

This landmark study, which turned out to be so influential in directing the course of future screening of anticancer drugs, was the culmination of many years of meticulous research in the Eagle and Foley laboratories. These previous studies had delineated the specific amino acid, salt, vitamin, and serum requirements for tissue culture of human and mouse cells (5, 6), leading to the formulations that are now known as the various forms of “Eagle’s Medium.” The development of defined media for growing cells in monolayer culture was a major advance.

The extensive study published by Eagle and Foley in Cancer Research in 1958 was actually an outgrowth of a seminal, but narrower, investigation they had published in 1956 in the American Journal of Medicine (7). In this latter article, they had shown that 13 drugs with known anticancer activity in vivo against transplanted tumors were also markedly cytotoxic in cell culture when tested against several tumor cell lines. The active compounds included amethopterin (methotrexate) and 6-mercaptopurine. In their 1956 summary, Eagle and Foley suggested that tissue culture methodology could be useful as a routine screening method for new anticancer drugs, and they then proceeded to perform the more extensive testing of the 180 compounds, which was published in 1958.

Eagle and Foley’s approach to first-pass screening of new anticancer drugs in cell culture, as predicted, soon became an accepted modality, and it continues to be so to the present day. Clearly, we now realize that the overall context of cancer is much more complicated than the mere growth of isolated tumor cells and that the tumor microenvironment is an essential feature of any malignancy. The essential role of inflammation, immune, and vascular cells in regulating the progression and metastasis of malignancy (8, 9) could barely be foreseen in 1958. Moreover, screening in cell culture also ignores the fundamental problem of tumor heterogeneity (10). In spite of these limitations, Eagle and Foley clearly foresaw a fundamental and critical problem that has continued to plague cancer chemotherapy right up to the present time. They made the important observation that active anticancer drugs also can cause equivalent cytotoxicity to nonmalignant, as well as malignant cells. Hopefully, new advances in developing targeted therapies that are not cytotoxic will eventually eliminate this problem altogether, but this is still a pressing issue in modern cancer chemotherapy.

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