Controlling genes via tetracyclines: Is the approach applicable in doping?

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Tetracycline regulatable transcription control systems are most widely and successfully used tools für controlling gene expression in many eukaryotic cells and organisms (1, 2). The main reasons fo their broad applicability (3) are the exceptional properties of the tet repressor/operator/inducer system. Particularly the fact that inducers like tetracycline and many of its derivatives are widely used antibiotics with a superb specificity provides a wealth of information on the chemistry and pharmacology of this class of substances. Accordingly, a panel of non-toxic and weIl characterized effector compounds is available.

More recently, our laboratory has developed a family of tetracycline controlled transcriptional activators and silencers with new specificities which can be used individually or in combination. Together, these elements enhance our capabilities of controlling one or several target genes upon transfer into cells or whole o!ganisms (4).

Transfer of the Tet regulatory systems to mammals including mice, rats and non-human primates hag allowed to control gene expression tightly and reversibly over long periods of time. Using proper promoters driving tetracycline controlled transactivators, Tet regulation may be restricted to single cell types such as hepatocytes or muscle cells (5). Moreover, the kinetics of gene activation and inactivation are fast (6). Results obtained with rodents suggest that the Tet systems may also be suitable für applications in gene therapy. Thus - as shown in the mouse model - the activity of therapeutic genes may be adjusted to relevant levels which can be modulated over long periods of time (7, 8). In this context, the panel of tetracycline controlled transcriptional regulators available and the choice of different effector substances appears useful for future developments.

Approaches being developed für gene therapy may well qualify für misuse in the field of doping. The goal to control quantitatively and reversibly EPO in respective patients may appear particularly attractive and results obtained in animal models suggest that indeed such approaches hold promise (7). As the transfer of such controlled expression units may occur at the level of DNA, e.g. into skeletal muscle via single injections, it may be difficult to develop diagnostic means which unequivocally identify respective mistige.

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