


# Chapter 6

## Cutting–Edge in Vitro Models and Multi–Omics Approaches for Carcinogen Exposome Studies

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### ABSTRACT

*The exposome concept has complemented the genome by opening new areas for cancer research. The in vitro models used in this context are fundamental for unraveling the molecular and cellular effects of carcinogenic agents in a controlled environment. Moreover, these models offer a new possibility for investigating the key mechanisms of tumor initiation and progression, bridging the gap between epidemiological data and mechanistic studies. In the same way, integrating recent technologies such as multiomics (genomics, transcriptomics, proteomics, metabolomics, etc.) expands the horizon for a deep understanding of cellular responses to carcinogenic exposures. This chapter reviews recent cutting-edge advances in using experimentation mod-*

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*els to study the carcinogenic exposome. It emphasizes their role in understanding carcinogenesis pathways, focusing on the most up-to-date technologies.*

## **INTRODUCTION**

It is increasingly clear that cancer is a multifactorial disease, in which environmental factors play the crucial role in its appearance and progression. Daily exposure to harmful pollutant molecules induces stress that generates abnormal physiological responses with the potential to cause health anomalies, and above all increase serious disorders.

Cancer, on average, is heritable by approximately 10%, while non-genetic factors, such as environmental exposures, are not. The wide spectrum of harmful molecules to which humans are exposed on an everyday basis - food, environment, stress, life-style - is largely unknown and unmeasured. Yet gene-environment interactions may account for most of this missing heritability of cancer (Young et al., 2025) hence the interest in exposome research, which aims to explore exhaustively the non-genetic causes of diseases, including cancer.

Those harmful molecules influence cancer appearance and metastasis which are crucial components of carcinogenesis. They trigger epithelial-mesenchymal transition (EMT), a step essential for cancer cell migration and invasion, and may directly alter metastatic pathways. Additionally, xenobiotics can change the tumor microenvironment and may lead to an accelerated spread of cancer and cells capacity to escape the original tumor.

In this chapter, we give a summary of current state-of-the-art developments in the use of experimental models for the investigation of carcinogenic exposures. It highlights the importance of comprehending carcinogenesis pathways, finding novel biomarkers, and refining risk prediction techniques. It emphasizes their role for understanding carcinogenesis pathways, identifying new biomarkers and optimizing risk prediction strategies. Furthermore, a particular focus is devoted to the most up-to-date technologies, such as organ-on-chip, for improving interactions between the exposome and the tumor microenvironment. Finally, this chapter will discuss the strengths and limitations of current approaches, while proposing new perspectives for improving in vitro models and suggesting potential lines of research for a better understanding of the cumulative impact of exposures in the context of exposomic cancer.

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