REVIEW (Research given the Yokohama City University Medical Research Prize for 2009)

The morphologic atypism of epithelial neoplasms
– its molecular basis and pathobiologic significance –

Koji Okudela
Department of Pathology, Yokohama City University Graduate School of Medicine

Abstract

"Atypism/atypia (atypism)" is defined as morphological differences between pathologic and normal conditions, and is generally used to describe morphological changes of neoplastic cells and tissues. It consists of various elements, the combination of which produces recognizable morphological differences between neoplasms and healthy tissues. This review discusses the inner meaning of each element of atypism by considering its possible biological significance and molecular basis based on recently established molecular biological mechanisms of cellular and tissue morphogenesis.

INTRODUCTION

The term "atypism/atypia (atypism)" the morphological differences between cells/tissues under pathologic and normal conditions1), is generally used to describe morphological changes to neoplastic cells and tissues. Elements of atypism are roughly subdivided into cellular and architectural changes. The former includes enlargement of cells, nuclei and nucleoli, an increase in the nuclear/cytoplasmic ratio, irregularity of chromatin patterns and the nuclear outline, prominent nucleoli, multiplicity of nuclei and nucleoli, and considerable polymorphism3). The latter includes change to the organization of tissue architecture, possibly resulting from a loss or instability of polarity and/or intercellular junctions of neoplastic cells1,2). Thus, atypism consists of a variety of elements, the composition of which produces recognizable morphological differences between neoplasms and healthy tissues. Atypism is important to the diagnosis and grading of neoplasms and also provides pathologists with extensive information. Thus, it is of great interest to understand its potential significance and molecular basis.

Recent advances in molecular and cellular biology have uncovered many factors essential for maintaining the integrity of cellular and tissue morphology, and also elucidated the underlying mechanisms. However, the cause and mechanism of atypism have not been investigated intensively.

This review discusses the possible causes, mechanisms, and biological significance of atypism, based on established factors and mechanisms maintaining the integrity of cellular and tissue’s morphology.

CELLULAR ATYPIISM

Enlargement of cells

Most neoplastic cells are enlarged compared to their non-neoplastic counterparts. Cellular overgrowth and degeneration are considered possible causes of the enlargement. Mucinous degeneration, possibly due to hyper-production of mucin and/or a defective mucin-releasing system, is a cause of increased volume in gastric signet ring cell carcinoma1,2). Similarly, glycogenic or lipid degeneration can increase cellular size in certain types of carcinoma, such as sugar tumors and renal cell carcinomas1-3). However, such degenerative changes are found only in specific types of neoplasms2-4). Thus, excessive growth is considered essential to the enlargement of neoplastic cells. Hyper-translation is one cause of excessive growth. The translational process is modulated by complex mechanisms involving many regulators. mTOR, first identified as an endogenous protein targeted by the antibiotic, Rapamycin, is one of the most important factors in translational regulation5,6). mTOR has

Koji Okudela, Department of Pathology, Yokohama City University Graduate School of Medicine, 3-9, Fukuura, Kanazawa-ku, 236-0004, Yokohama, Japan