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Ex vivo study of MAPK profiles correlated with parameters of apoptosis during cervical carcinogenesis

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Abstract

Cervical cancer is a leading cause of death in developing countries and is the second highest occurring cancer in women all over the world. The progression of cancer is a multistep process affecting aspects of cellular function such as proliferation, differentiation and apoptosis. Mitogen activated protein kinases (MAPKs), which include p38-MAPK, c-Jun NH_2-terminal kinase (JNK) and extracellular signal-regulated kinases (ERKs) are closely associated with cell proliferation and apoptosis and the balance between them could determine a cell's fate. Despite the expanding research effort in vitro, little is known about MAPK activation in clinical specimens of cervical cancer. Therefore, the aim of this ex vivo study was to correlate the phosphorylation status (activity) of MAPKs (p38-MAPK, JNK and ERK), as well as poly (ADP-ribose) polymerase (PARP) and caspase-3 (two cellular markers of apoptosis), during the different stages of cervical carcinogenesis, to observe whether correlations between MAPK activities and apoptosis during the disease process exist. Decreased p38-MAPK phosphorylation was found in the carcinoma (Ca) group) compared to the normal tissues, as well when the low grade squamous intraepithelial lesion—LSIL) group and high grade squamous intraepithelial lesion—HSIL) group were compared with the Ca group. Interestingly, a significant decrease in ERK44 phosphorylation was observed in Ca when compared to LSIL and HSIL. There was also a significant decrease in JNK phosphorylation in Ca when compared with normal tissue and HSIL. As expected, caspase-3 activation and PARP cleavage was significantly lower in Ca when compared with normal tissue. Our results present the first evidence of in vivo involvement of MAPKs in cervical cancer and indicate a possible correlation between MAPK activities and apoptosis in the disease process.
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Keywords: MAPKs; Apoptosis; Cervical carcinogenesis

Abbreviations: MAPK, mitogen activated protein kinase; P38-MAPK, p38-mitogen activated protein kinase; JNK, c-Jun NH_2-terminal kinase; ERK, extracellular signal regulated kinase; PARP, poly (ADP-ribose) polymerase; LSIL, low grade squamous intraepithelial lesion; HSIL, high grade squamous intraepithelial lesion; Ca, carcinoma; N, normal.

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1. Introduction

Cancer of the cervix constitutes about 1.7% of all cancers [1]. In developing countries this tumor is still a leading cause of mortality in relatively young women. However, this cancer is not limited to third world countries and is the second highest occurring cancer in woman all over the world [2]. Over the years, ongoing research contributed to the assessment of cervical carcinogenesis. Vigorous research already identified cell signaling pathways and specific family members of transcription factors involved during carcinogenesis in the case of several cancer types. Because of the many important cellular functions controlled by mitogen activated protein kinases (MAPKs), they have been subjected to extensive investigation to define their roles in human diseases [3]. It has been shown that MAPKs mediate signaling cascades leading to COX-2 induction and are important regulators in signaling pathways leading to oncogene expression during tumorigenesis and carcinogenesis, associated with cell proliferation and apoptosis [3–6]. Inhibition of cell proliferation and induction of apoptosis in tumors and cancers are crucial steps on which cancer therapy is based. Therefore, MAPK activities and apoptosis during cervical carcinogenesis were further explored in this study.

A brief overview on MAPK signaling pathways associated with cell proliferation and apoptosis, as encountered in the literature, is given. Regulation of cell growth is mediated by a complex array of signaling pathways precisely coordinated by different families of cell surface receptors. These signaling pathways regulate all the critical phases of cell growth including cell proliferation, differentiation and apoptosis [7]. In many instances, the signal coupling between the receptors and the nucleus is mediated by a series of sequentially activating protein kinases. MAPKs are serine/threonine kinases activated by dual phosphorylation on both a tyrosine and a threonine residue [8]. The three well-known mammalian MAPKs, namely extracellular signal-regulated protein kinase (ERK), p38-MAPK and c-Jun NH_2-terminal protein kinase (JNK) play a pivotal role in the transmission of signals from the cell surface receptors to the nucleus [9]. Each of these kinases is a target for discrete but closely related phosphorylation cascades in which a sequential activation of three kinases constitutes a common signaling module [10,11]. The best characterized MAPK pathway is the Ras/Raf/MEK cascade leading to the activation of ERK1/2 in response to growth factors [8]. The ERK signaling cascade is triggered by growth factors, mitogens and hormones leading to cell proliferation [12–14]. This proliferation is achieved by the activation of a variety of targets including Elk-1, a transcription factor. Persistent signaling of ERKs, however, will lead to growth arrest [15]. On the other hand, the p38-MAPK and JNK families appear to be pro-apoptotic in many cell types, however, their exact roles in regulating cell death are unclear [16,17]. Further evidence, which links p38-MAPK and JNK to apoptosis, is the finding that their signaling pathways are associated with activation of effector caspases, including caspase-3 [18]. Caspase-3 cleaves several substrates, including poly (ADP-ribose) polymerase (PARP), lamins and actins with resultant chromosomal degradation and cellular morphological changes characteristic of apoptosis [19–22].

There is increasing evidence that the MAPKs are important role players in tumorigenesis and carcinogenesis. A dynamic balance between JNK, p38-MAPK and ERK activation will determine the cellular response, either cell growth or death [23]. Although several in vitro studies indicated disturbances in the activation of the MAPKs on different tumor entities, including HeLa cells [13,14,24–29], there are no indication whether the activation/inhibition of these MAPK in vitro can be extrapolated to the ex vivo situation. Therefore, an ex vivo study of MAPK activation correlated with cellular markers of apoptosis in cervical carcinogenesis, as a sound basis for therapeutical approaches in the prevention and treatment during the disease process, definitely is required and served as motivation for this study.

2. Material and methods

2.1. Materials

Ethical approval for this project was obtained from the ethics committee of the University of Stellenbosch (Faculty of Health Science) and conforms to the Guide for the Care and Use of Laboratory Animals,

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