Clinical implications of basic science

Oncogenic Viruses: A review of Epithelial Mesenchymal Transition (EMT) as a metastatic tool in viral induced cancers

Muhammad Asif Qureshi, Shams Nadeem Alam
Dow University of Health Sciences, Karachi, Pakistan

ABSTRACT

Objective

To summarize current knowledge on induction of Epithelial-Mesenchymal-Transition (EMT) during viral oncogenesis.

Methods

Publications describing “induction of EMT in viral induced cancers” were retrieved from Pubmed database and managed in the End Note software (version XIII) for further analysis.

Results

Some oncogenic viruses like EBV, HPV, HBV, HCV, and adenoviruses have recently been shown to switch on the EMT-programming prior to tumor invasion. Various proteins
involved in viral induced EMT include TGFβ, NFκB, Smad3, Cadherins, Catenins and Hbx, amongst others.

Conclusion

Epithelial-Mesenchymal-Transition has been involved as metastatic tool by oncogenic viruses. We recommend further research on the topic to fill the existing gaps. (Rawal Med J 2011;36:317-321).

Keywords

Oncogenic viruses, EMT, tumor invasion, metastasis.

INTRODUCTION

Cancer is a major cause of death worldwide responsible for more than 7.6 million deaths a year.\(^1\) It is a multifactorial disorder that is influenced by several factors including genetic, environmental and infectious agents such as viruses. Concept of viral induced cancers emerged when Borrel in 1903 proposed a theory pointing towards viral association of cancers.\(^2\) With extensive research, virally induced malignancies now include hepatocellular carcinoma (HCC) and cholangiocarcinoma by Hepatitis C virus (HCV),\(^3\) cervical cancer by Human Papilloma virus (HPV),\(^4\) and nasopharyngeal carcinoma (NPC) by Epstein-Barr virus (EBV),\(^5\) amongst others.

Regardless of the etiology, loss of basement membrane, tumor invasion and metastasis are the major hallmarks of cancer. Conversion of a normal cell to malignant invader is a dynamic process and the mechanisms involved in the process have started to unravel only recently. Invasion and metastasis is a very complex event and various oncogenic insults may
undertake different biochemical routes within a cell to render it malignant. Epithelial mesenchymal transition (EMT) is one of such programs, enabling epithelial cells to become malignant and invasive. During EMT, epithelial cells change their biological and metabolic profiles and switch on anti-apoptotic, invasive and proliferative programs. It is characterized by expression of several mesenchymal and/or stem cell markers including TGFβ, Twist, Bim1, ABCG2, Nanog, Sox2, vimentin and loss of E-Cadherin.

It is interesting that recently some of the oncogenic viruses (EBV, HPV, HBV, HCV, and adenoviruses) have been reported to induce the EMT as part of their oncogenic processes. Of note, viruses can induce the EMT even in various benign disorders. For example, EBV is shown to induce EMT in an in vitro model of idiopathic pulmonary fibrosis (IPF). Human immune deficiency virus (HIV) associated nephropathy (HIVAN) has also been proposed to be associated with EMT. EMT is also known to be involved in the pathogenesis of polyomavirus induced nephropathy. As mentioned earlier, EMT is a rapidly growing discipline and its association with several malignancies is becoming increasingly apparent. Basic molecular mechanisms involved in EMT and its association with various cancers have been reviewed in detail elsewhere, and are not the focus of this review. In this report, we review the present understanding of EMT induction during viral oncogenesis.

METHODS

We did retrieve all publications describing “induction of EMT in viral induced cancers” from Pubmed database and used End Note software (version XIII) for synthesis and analysis.
RESULTS

Induction of EMT by some of the oncogenic viruses is well studied; however, there are less studied oncolytic viruses that can induce EMT, such as adenoviruses.\textsuperscript{19}

**EBV and EMT**

EBV is a gamma herpes virus that primarily infects B – lymphocytes via CD21 receptors.\textsuperscript{20} It is associated with several malignancies including tumors of epithelial and lymphoid origin.\textsuperscript{21} Its genome harbors several oncogenes including latent membrane protein (LMP) 1, LMP2A and EBV nuclear antigen 1 (EBNA1).\textsuperscript{22} LMP1 is a primary EBV oncogene and is necessary for fibroblast transformation in vitro,\textsuperscript{23} and is most tightly associated with epithelial origin nasopharyngeal carcinoma (NPC).\textsuperscript{24} Metastasis is a major clinical presentation of NPC\textsuperscript{25-27} and can occur as early as 18 months after the appearance of first symptom.\textsuperscript{28}

**Table 1. Various oncogens involved in EMT.**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Oncoprotein</th>
<th>Induces EMT via</th>
<th>EMT Markers</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBV</td>
<td>LMP1</td>
<td>NFkB</td>
<td>Twist</td>
<td>9,11</td>
</tr>
<tr>
<td></td>
<td>LMP2A</td>
<td>Akt</td>
<td>Bim1,ABC2G</td>
<td>10</td>
</tr>
<tr>
<td>HCV</td>
<td>Core protein</td>
<td>Smad3</td>
<td>Nanog, Sox2</td>
<td>12,13</td>
</tr>
<tr>
<td>HBV</td>
<td>Hbx</td>
<td>c-Src</td>
<td>LOXL2,TGFB</td>
<td>34,35</td>
</tr>
<tr>
<td>HPV16</td>
<td>E6</td>
<td>PDZ</td>
<td>Vimentin, E cad,</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>E7</td>
<td></td>
<td>Fibronectin</td>
<td>42</td>
</tr>
</tbody>
</table>
Exact molecular events that lead to invasion in NPC patients are largely unclear. Although NPC metastasis can occur in the absence of EBV,\textsuperscript{29} it is interesting that LMP1 can use EMT as an invasive program.\textsuperscript{9,11} LMP2A, another EBV oncoprotein, is also known to induce EMT as part of its oncogenic progression.\textsuperscript{10} However, most of the details regarding EBV induced EMT are unknown, there is some evidence that NFkB, Akt and TGFβ play a role in this signaling pathway.\textsuperscript{9-11}

**HBV, HCV and EMT**

HCV infection has a known association with HCC.\textsuperscript{30} HCV core protein induces EMT during the pathogenesis of cholangiocarcinoma via an intermediate molecule called LOXL2,\textsuperscript{12} which is known to induce metastasis and invasion.\textsuperscript{31} In addition to LOXL2, TGFβ is another HCV core protein target that is utilized in EMT induction.\textsuperscript{13} TGFβ is an interesting molecule that exerts varying range of functions under different circumstances. It can have tumor suppressor as well as tumor promoting functions depending upon the upstream signaling.\textsuperscript{32,33} TGFβ shift of functions towards invasive profile by HCV is an interesting observation and opens up a new era in this field of research.
Figure 1: Schematic representation of EMT induction by oncogenic viruses.

Pathways involved in induction of EMT by EBV, HBV, HCV and HPV. LMP1, LMP2A, Hbx, HCV core protein, E6 and E7 are the oncogenes involved in EMT induction. Several pathways and signaling mechanisms involved in EMT are shown.

There are a couple of studies suggesting that EMT is also induced by HBV. Involvement of Hbx protein of HBV in EMT induction was reported in a liver tumor cell line SMMC-7721.\textsuperscript{34} Using similar cell line, it has also been shown that the Hbx related EMT induction is modulated by activation of a proto-oncogene, c-Src.\textsuperscript{35} Furthermore, a protein called periostin is also found involved in the induction of EMT in bile duct as well as HCC.\textsuperscript{36} However, its association with HBV and/or HCV is not fully understood till date.
**HPV and EMT**

HPVs are DNA viruses that are divided into high risk (type 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66), and low risk genotypes (all others). E6 and E7 are HPV oncogenes that are expressed in almost all cervical cancers and are both known to induce EMT. HPV18 E6, at its C terminus has a domain called PDZ domain. Interaction of this domain with various PDZ domain containing proteins and subsequent degradation is thought to play a crucial step in oncogenic potential of HPV induced carcinogenesis. Recently, it is reported that E6 degradation of PDZ domain containing proteins is responsible for EMT induction and subsequent invasion. Of note is the fact that the reported induction of EMT by various oncogenic viruses needs to be analyzed in greater depths. Interestingly, a study on various isotypes of HPV revealed that HPV induced EMT induction in keratinocytes could be affected by the factors present in growth media. These findings could provide new dimensions regarding the more appropriate experimental conditions for EMT related *in vitro* studies.

**DISCUSSION**

Understandings of the signaling pathways utilized by the viruses to induce malignancies are yet not fully understood. Huge amounts of research and funds in this research area are contributing rapidly to our understanding. The basic idea is that, if viruses have a strong association with cancers, or at least some types of cancers, it might be possible to diagnose and treat malignancies relatively earlier and hence the survival of the patients can be increased. Several examples exist in the literature establishing a link between antiviral
treatment and reduction in cancer associated morbidity and mortality. For example, treatment of HCV associated hepatitis has shown reduction in progression to HCC.\textsuperscript{40}

Various markers of EMT are summarized in Table 1. NFkB is a seminal molecule in several biological process including inflammation, cellular stress, free radical associated injury and oncogenesis amongst others.\textsuperscript{41} A large number of molecules are involved in NFkB signaling including Ras, NIK and Akt which his itself a molecule involved in EBV induced EMT. Activation of NFkB and Akt in EBV induced EMT suggests possible involvement of other proteins associated with NFkB and AkT pathways (Fig 1). Such associations can be exemplified by the involvement of Twist, Bim and ABCG2 in viral induced EMT. TGF\beta, another central molecule in several pathological conditions is also found involved in HCV induced EMT. Furthermore, induction of proto-oncogenes such as c-Src also suggests direct involvement of EMT in viral induced oncogenic processes. Involvement of Smad3 and PDZ by HCV and HPV respectively also needs further exploration.

Identification and characterization of EMT in viral induced cancers brings into light a novel mechanism that an oncogenic virus can utilize to initiate the oncogenic event. Identification of such markers of EMT in various viral associated cancers can provide novel diagnostic as well as therapeutic targets. This opens up a question that what happens if this viral induced EMT is inhibited? For example, inhibition of downstream effectors like LOXL2, Twist and their effects on pathogenesis still remains an open question. With a small number of studies at present, it is difficult to draw a full picture but these pieces of information builds the skeleton that needs to be filled in by further research.
CONCLUSION AND RECOMMENDATIONS

Viral induced Epithelial-Mesenchymal-Transition as a very important and yet largely unaddressed and ill understood issue. There are only few studies available pointing towards EMT induction by viruses as their metastatic tool. We strongly recommend further studies on this topic to contribute more understanding towards the field of viral oncology.

Correspondence: Muhammad Asif Qureshi. Email: m.qureshi.1@research.gla.ac.uk

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REFERENCES


