

# **Biomarkers of epithelial-mesenchymal transition: E-cadherin and beta-catenin in malignant transformation of oral lesions**

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## ABSTRACT

**Objective:** Detecting oral lesions at high-risk of becoming cancer may contribute to early intervention of oral cancer. The diagnosis of dysplasia in an oral lesion is used to predict this risk but is subject to interobserver and intraobserver variability. Studying biomarkers or molecular markers that reflect underlying molecular alterations can serve as an additional and objective method of risk assessment. E-cadherin and beta-catenin, molecular markers of epithelial-mesenchymal transition (EMT), potentially contribute to early malignant progression in oral tissue. This narrative review provides an overview of EMT, its relation to oral cancer, and the interaction among E-cadherin, beta-catenin, and the Wnt pathway in malignant progression of oral tissue. **Methods:** Full-text literature concerning EMT, E-cadherin, beta-catenin, oral epithelial dysplasia, and oral cancer was reviewed from PubMed and Google Scholar. **Results:** Sixty original research articles, reviews, and consensus statements were selected. **Discussion:** EMT, a biological mechanism characterized by epithelial and mesenchymal changes, can contribute to cancer development. Molecular markers of EMT including TWIST, vimentin, and N-cadherin may serve as prognostic markers of oral cancer. Dependent on Wnt pathway activity and the loss of membranous E-cadherin, E-cadherin and beta-catenin can have various roles along the spectrum of malignant progression, including tumour inhibition, early tumour progression, and late-stage tumour progression. Cross-sectional immunohistochemical research has found changes in expression patterns of E-cadherin and beta-catenin from normal oral tissue, oral epithelial dysplasia, to oral squamous cell carcinoma. **Conclusion:** Future research should explore the longitudinal role of EMT markers in predicting malignant progression in oral tissue.

**Keywords:** epithelial-mesenchymal transition, cadherins, beta catenin, oral epithelial dysplasia, malignant transformation, neoplasms, risk, mouth

**CDHA Research Agenda category:** risk assessment and management

CDHA In Press

## INTRODUCTION

In 2020, there were almost 400,000 new cases of cancers of the lip and oral cavity worldwide.<sup>1</sup> In the United States alone, in 2021 there was an estimate of over 50,000 new cases and 10,000 deaths (oral and pharyngeal cancer).<sup>2</sup> In Canada, there is a 64% five-year survival rate for oral cancer,<sup>3</sup> with an estimated 7500 new cases of head and neck cancer and 2100 deaths in 2022.<sup>4</sup> Despite the continuous advances in research and technology, new cases and deaths of oral cancer still arise. This is because late-stage diagnosis of this disease results in high treatment-related morbidity.<sup>5</sup> Research efforts must focus on early detection and intervention of oral cancer for improved patient survival rates.<sup>5</sup>

An oral lesion's risk of becoming cancer is assessed based on patient demographics and risk habits, and clinical and histological findings of a lesion.<sup>6</sup> Currently, the gold standard for determining a lesion's risk is diagnosing the presence and severity of dysplasia.<sup>7</sup> Dysplasia is diagnosed based on architectural and cytological changes in the epithelium that show an increased risk for malignant progression. Architectural changes include abnormal epithelial stratification, drop-shaped rete ridges, mitosis high in the epithelium, generalized premature keratinization, keratin pearls within rete ridges, and the loss of epithelial cell cohesion and polarity in basal cells. Additional architectural changes include a sharply defined margin to changes, an expanded proliferative compartment, altered keratin pattern for oral sub-site, verrucous or papillary architecture, changes extending to minor gland ducts, multiple different patterns of dysplasia, multifocal or skip lesions, and basal cell clustering or nesting. Cytological changes include abnormal mitotic figures, apoptotic mitoses, single cell keratinization, hyperchromasia, increased nucleus to cytoplasm ratio, increased number and size of nucleoli, and irregular cell and nucleus size and/or shape.<sup>7</sup>

Although histological diagnosis of dysplasia is important in determining a lesion's risk, it comes with limitations. There is often interobserver and intraobserver variability in the diagnosis of dysplasia due to the lack of uniform and specific diagnostic criteria.<sup>8</sup> Due to this limitation, studying biomarkers or molecular markers may provide an additional and objective avenue for assessing a lesion's risk for malignant progression.<sup>9</sup> As clinical and histological changes reflect underlying molecular events, molecular markers can indicate alterations during carcinogenesis.<sup>9</sup> A biological process that is indicated by multiple molecular markers is epithelial-mesenchymal transition (EMT). This process is marked by a progressive decrease in epithelial cell features and an increase in mesenchymal cell features.<sup>10</sup> It has been indicated to play a role in cancer development,<sup>11</sup> but may or may not contribute to early malignant progression, such as in dysplasia. One event of EMT that may play a part in both early and late malignant progression is the interaction of its molecular markers E-cadherin and beta-catenin in the Wingless/Integrated (Wnt) pathway.

This paper will review the basics of EMT, EMT's relation to oral cancer, and the interaction of E-cadherin, beta-catenin and the Wnt pathway in malignant progression and the oral tissue. A greater understanding of this topic may contribute to lesion risk assessment and future guidance of appropriate clinical management.

## **METHODS**

This narrative review selected full-text literature from PubMed and Google Scholar. Keywords used in the search include oral OR mouth\* OR lip\* OR tongue\* OR palate\* OR head and neck, cancer\* OR carcinoma\* OR malignan\* OR neoplasm\* OR tumor\* OR mass\*, E-cadherin\* OR uvomorulin\*, beta-catenin\*, and dysplasia\*. There were no restrictions on

publication dates to ensure necessary information was included. Publications not in English were excluded.

## **RESULTS**

Thirty-eight original research articles, 20 literature and narrative reviews, 1 systematic review, and 1 consensus statement were selected. TWIST, vimentin, and N-cadherin may be EMT markers prognostic for oral cancer based on their correlation with clinical features of oral cancer. Expression patterns of E-cadherin and beta-catenin change from normal oral tissue to oral squamous cell carcinoma and may be related to their interaction with the Wnt pathway, affecting different steps of malignant progression.

## **DISCUSSION**

### **EMT**

EMT was originally coined as the “epithelial-mesenchymal transformation” by Elizabeth Hay in 1995.<sup>12</sup> Modification of the term has occurred over the years, and EMT is now known as the “epithelial-mesenchymal transition” to represent the biological plasticity of this mechanism.<sup>11</sup> EMT features a loss of epithelial features and increase in mesenchymal traits.<sup>10</sup> Specifically, there is a loss of epithelial cell polarity, disruption to epithelial cell junctions, degradation of the basement membrane, and reorganization of the extracellular matrix.<sup>13</sup> As the cells gain mesenchymal features and increased motility, there is a loss of the cobble-stone arrangement in epithelial cells.<sup>13</sup> In EMT, cells exhibit both epithelial and mesenchymal features, and are rarely in a complete mesenchymal state.<sup>13</sup> Interestingly, EMT can be reversed in the process “mesenchymal-epithelial transition” (MET) where mesenchymal cells regain epithelial cell traits.<sup>11</sup>

EMT takes part in different biological contexts, which consequently categorizes it into three types. Type I EMT is involved in embryogenesis, implantation, and organ development.<sup>11</sup> Type II EMT plays roles in wound healing, tissue regeneration, and organ fibrosis. It typically occurs as a repair process following trauma or inflammation and stops once the repair process is complete. Type III EMT has been suggested as an important mechanism in cancer development. The mesenchymal characteristics gained increases motility of the cells and promotes invasiveness and metastasis. When cancer cells have reached distant organ sites, MET may facilitate secondary tumour formation and initiate colonization.<sup>11</sup> However, it is still unknown whether the occurrence of EMT is necessary for tumour cells to complete metastasis.<sup>14</sup>

EMT starts with the activation of EMT-inducing transcription factors (e.g. zinc finger E-box binding homeobox (ZEB), TWIST, and SNAIL), which promote and repress genes that facilitate epithelial and mesenchymal changes.<sup>13</sup> In addition to the activation of transcription factors, there is the expression of cell-surface proteins, reorganization and expression of cytoskeletal proteins, production of enzymes that degrade the extracellular matrix, and contribution to changes in expression of microRNAs.<sup>11</sup> The molecular markers of EMT that indicate these processes include transcription factors, cell surface markers, cytoskeletal markers, extracellular proteins, epigenetic markers, and microRNAs.<sup>11</sup> Common epithelial markers that are progressively lost include E-cadherin, cytokeratin, and laminin-1, and common mesenchymal markers that are increasingly gained include N-cadherin, vimentin, and beta-catenin.<sup>11</sup>

## EMT MARKERS IN ORAL CANCER AND DYSPLASIA

The following sections will include studies on immunohistochemical expression of prominent EMT markers in oral cancer and dysplasia. E-cadherin and beta-catenin will not be discussed in-depth here as they will be explored in the next section.

EMT-inducing transcription factors are upregulated in EMT. TWIST is a transcription factor that regulates organ development but is highly expressed in tumour cells in the oral tissue,<sup>15-17</sup> and has been suggested as a prognostic factor for oral cancer.<sup>17</sup> Zhou et al. show that TWIST expression may be correlated with clinical features of oral cancer including low differentiation, advanced clinical stage, lymph node metastasis, and local recurrence.<sup>17</sup> Other EMT-inducing transcription factors including SNAIL, ZEB1, and ZEB2 also show increased expression in oral cancer but the expression is less when compared to TWIST.<sup>16</sup> Göppel et al. suggest that in head and neck cancer, these transcription factors may play a less important role as compared to TWIST.<sup>16</sup> Vimentin, a type III intermediate filament, normally found in mesenchymal cells, is categorized as a cytoskeletal marker of EMT.<sup>10</sup> Vimentin is a potential prognostic factor for patients with oral squamous cell carcinoma (OSCC).<sup>18</sup> Liu et al. found that in squamous cell carcinoma of the tongue, high vimentin expression is associated with poor cell differentiation and lymph node metastasis.<sup>18</sup> Combined results of vimentin and E-cadherin expression show better prognostic significance than the prognostic value of these two proteins individually.<sup>19</sup> Monitoring expression levels of cadherins in EMT has been termed “cadherin switch.” The cadherin switch from E-cadherin to N-cadherin expression has been used to observe EMT in embryonic development and cancer.<sup>10</sup> In adult tissue, N-cadherin contributes to synapse function, vascular stability, and bone homeostasis.<sup>20</sup> It is expressed in neural cells, endothelial cells, stromal cells, and osteoblasts, but is absent or rarely expressed in normal epithelial cells.<sup>20</sup> In OSCC, high expression of N-cadherin and low expression of E-cadherin are closely related,<sup>21,22</sup> and is correlated with histological differentiation, pattern of invasion, and lymph node metastasis.<sup>21</sup> Thus, the cadherin switch from E-cadherin to N-cadherin has been suggested to play a role in cancer development and serve as a prognostic factor.<sup>18,21,22</sup>



Freitas de Morais et al. recently published a systematic review on the immunohistochemical expression of EMT markers in oral epithelial dysplasia (OED).<sup>23</sup> With increasing grades of OED, they found a gain in nuclear transcription factors and mesenchymal markers along with a decrease in epithelial and cell adhesion markers. Specifically, they noted a loss of the cell-adhesion marker claudin-1. Similar to studies on TWIST in oral cancer, there was an increase in TWIST expression in OED, while other EMT-inducing transcription factors need further research. Currently, there is an absence of research on epigenetic EMT markers in OED. Longitudinal research is needed to associate EMT with the risk of malignant transformation of potentially malignant oral lesions.<sup>23</sup>

#### E-CADHERIN AND BETA-CATENIN

One of the main events of EMT is the loss of E-cadherin.<sup>10,11</sup> E-cadherin is a classical cadherin encoded by the CDH1 gene.<sup>24</sup> Cadherins are molecules characterized by extracellular cadherin repeat domains and are dependent on homophilic  $\text{Ca}^{2+}$  for maintaining cell-to-cell adhesion.<sup>25,26</sup> Classical cadherins feature five extracellular cadherin repeats and is a major component of the adherens junctions, which are junctions involved in epithelial cell-to-cell connections.<sup>27,28</sup> Adherens junctions are composed of a classical cadherin (e.g. E-cadherin), beta-catenin, alpha-catenin, and p120-catenin.<sup>27</sup> Because the loss of E-cadherin leads to the lack of epithelial cell adhesion, its loss is often thought to contribute to the latter stages of cancer development, such as invasion and metastasis.<sup>29</sup> E-cadherin loss may result from mutation, epigenetic changes, proteolytic cleavage, degradation, or transcriptional repression (e.g. by EMT-inducing transcription factors).<sup>24,30</sup> Some authors have proposed that the loss of E-cadherin may also contribute to early malignant progression via beta-catenin signaling through the canonical Wnt pathway, which will be referred to as the Wnt pathway in the remainder of this text.<sup>31,32</sup>

Beta-catenin's role in the Wnt pathway will be discussed in the following section. Like E-cadherin, beta-catenin is responsible for cell adhesion.<sup>33</sup> It is an Armadillo repeat protein that binds E-cadherin to alpha-catenin, which is bound to the actin cytoskeleton to maintain cell adhesion.<sup>33</sup>

## **The Wnt pathway**

The Wnt pathway is active in adult tissue homeostasis and stem cell renewal, cell proliferation, and cell differentiation during embryonic development.<sup>34,35</sup> When this pathway is deregulated, it can lead to diseases such as cancer.<sup>34,35</sup> A simplified overview of the Wnt pathway will be given in this section.

When the Wnt pathway is inactive, a destruction complex consisting of Axin, adenomatous polyposis coli (APC), glycogen synthase kinase 3 (GSK-3), casein kinase 1 (CK1), and protein phosphatase 2A (PP2A) initiates the degradation of beta-catenin.<sup>32,36</sup> As a result, beta-catenin accumulation in the cytoplasm and translocation to the nucleus to affect Wnt target genes does not occur.<sup>32</sup> There are high amounts of membranous beta-catenin compared to cytoplasmic and nuclear beta-catenin.<sup>32</sup>

During Wnt pathway activation, Wnt proteins bind to the Frizzled (FZD)/low density lipoprotein receptor-related protein (LRP) complex on the cell surface, which destroys the destruction complex.<sup>32</sup> There is no degradation of beta-catenin, which leads to an accumulation of beta-catenin in the cytoplasm and eventual translocation to the nucleus. In the nucleus, beta-catenin interacts with the T cell-factor/lymphoid enhancer-binding factor (TCF/LEF) transcription factors to activate Wnt target genes involved in cancer formation (i.e. c-myc, cyclin D1, and survivin).<sup>32,37-39</sup>

During embryogenesis and tissue homeostasis, the Wnt pathway is normally activated through binding of Wnt proteins.<sup>32</sup> In disease, dysregulation of the Wnt pathway can be caused by mutations, but mutations for beta-catenin, Axin 1, and APC are not common in oral malignancy.<sup>40,41</sup> Other processes that may dysregulate the Wnt pathway in OED and OSCC include an increase in Wnt ligands, interactions with other pathways, epigenetic alterations, endosomal sequestration of the destruction complex, and etiological factors.<sup>42-49</sup>

### **E-cadherin and beta-catenin in the Wnt pathway**

E-cadherin and beta-catenin in the Wnt pathway can contribute to different aspects of malignant progression depending on the loss of E-cadherin at the cell membrane and whether the Wnt pathway is active. Their role will be discussed in three parts: A) inhibition of tumour progression, B) early tumour progression, and C) late-stage tumour progression (Figure 1 and Figure 2).

#### *A) Inhibition of tumour progression*

In this context, E-cadherin is present at the cell membrane. Regardless of the Wnt pathway being inactive or active, beta-catenin is still bound to E-cadherin at the cell membrane.<sup>31</sup> Since E-cadherin and beta-catenin are bound together, cell-to-cell adhesion is maintained and E-cadherin acts as a tumour suppressor (A in Figure 1 and Figure 2).<sup>31</sup>

#### *B) Early tumour progression*

For this scenario and the one following, there is a loss of E-cadherin at the cell membrane (e.g. during EMT) and thus a release of beta-catenin from the cell membrane to the cytoplasm.<sup>31,50,51</sup> In this scenario, the Wnt pathway is active. Beta-catenin accumulated in the cytoplasm will translocate to the nucleus to affect Wnt target genes involved in carcinogenesis.<sup>31</sup>

Jeanes et al. propose that the loss of E-cadherin can amplify Wnt signaling when the Wnt pathway is active.<sup>31</sup> Thus this scenario may play a role in early tumour progression, such as in dysplasia (B in Figure 1 and Figure 2).<sup>50</sup>

### *C) Late-stage tumour progression*

This scenario also involves the loss of E-cadherin at the cell membrane and consequently an increase in cytoplasmic beta-catenin, but with an inactive Wnt pathway. Since the Wnt pathway is inactive, the destruction complex is intact, and the influx of beta-catenin in the cytoplasm is destroyed. Beta-catenin does not translocate to the nucleus to affect Wnt target genes involved in malignant progression.<sup>31,50</sup> However, because there is a loss of E-cadherin and beta-catenin at the cell membrane, the adherens junction is incomplete and there is a loss of cell-to-cell adhesion, which may contribute to the latter half of tumour progression (i.e. invasion and metastasis) (C in Figure 1 and Figure 2).<sup>50</sup>

### **E-cadherin and beta-catenin expression in normal oral mucosa (NOM), OED, and OSCC**

Williams et al. in 1998 was the first to report the expression patterns of E-cadherin and beta-catenin in OED.<sup>52</sup> Their early results were based on staining intensity and expression patterns, but are similar to the findings of current studies.<sup>52</sup> The details of E-cadherin and beta-catenin expression in NOM, OED, and OSCC in the current literature are discussed in-depth in the author's (I.Y.) thesis, but will be discussed briefly in this review.<sup>53</sup>

### *E-cadherin expression in oral tissue*

In studies performing immunohistochemical analysis, a progressive decrease in membranous E-cadherin expression is evident from NOM, OED, to OSCC (Table 1).<sup>52,54-61</sup> There is also reduced membranous E-cadherin expression in progressing severities of OED, but

not all studies showed significant results.<sup>57,58</sup> Chaw et al. proposed that in their study, the insignificant decrease in E-cadherin expression from NOM, mild OED, moderate-severe OED, to OSCC may indicate that tumour cells are in a “semi-mesenchymal” state and thus cells may not exhibit complete mesenchymal characteristics, including an increased loss of E-cadherin.<sup>58</sup> In addition to a loss of membranous E-cadherin, an increase in cytoplasmic E-cadherin may be observed; however, mainly in OSCC.<sup>52,55,59–61</sup> It has been suggested that cytoplasmic expression of E-cadherin in tumour cells represents a state where E-cadherin is no longer functional or useful to the cell.<sup>59,62</sup>

#### *Beta-catenin expression in oral tissue*

Immunohistochemical research on beta-catenin expression has shown a decrease in membranous beta-catenin and an increase in cytoplasmic and nuclear beta-catenin from NOM to OED (Table 2).<sup>42,52,54,58,61,63–66</sup> In NOM, beta-catenin is expressed mainly in the cell membrane.<sup>52,58,61,63,64,66</sup> In OED however, there is a decrease in beta-catenin expression in the cell membrane.<sup>54,58,65</sup> Studies have also found decreasing membranous beta-catenin expression with increasing severities of OED.<sup>58,65</sup> In addition to a decrease in membranous beta-catenin in OED, there is an increase in cytoplasmic and nuclear beta-catenin.<sup>58,61,63–65</sup> Of interest, Chaw et al. and Reyes et al. found an increase in cytoplasmic and nuclear beta-catenin expression in moderate and severe OED.<sup>58,64</sup> In OSCC, there is also a decrease in membranous beta-catenin and increase in cytoplasmic and nuclear beta-catenin when compared to NOM.<sup>42,52,54,58,61,64–67</sup> However, when comparing cytoplasmic and nuclear beta-catenin expression between OED and OSCC, some studies found a decrease in expression from OED to OSCC, whereas other studies found an increase from OSCC to OED.<sup>42,54,61,64</sup> Reyes et al. suggest that greater amounts of

nuclear beta-catenin in OED rather than OSCC plays an important role in cell proliferation in OED, contributing to early malignant progression.<sup>68</sup>

#### *E-cadherin and beta-catenin expression in oral tissue*

Studies show mixed results when analyzing the expression of E-cadherin and beta-catenin together. Kaur et al. found that a loss of membranous E-cadherin was significantly associated with a loss of membranous beta-catenin in oral leukoplakia and OSCC.<sup>54</sup> Expression of E-cadherin and beta-catenin analyzed separately and combined showed significant correlation with enhanced tumour invasiveness, late clinical stage, nodal metastasis, and poor prognosis.<sup>54</sup> However, in the results from Chaw et al., membranous E-cadherin and membranous or cytoplasmic/nuclear expression of beta-catenin were not significantly correlated.<sup>58</sup> They suggest that the translocation of beta-catenin to the nucleus may not be related to the loss of E-cadherin.<sup>58</sup>

#### GAPS IN THE RESEARCH

Due to the lack of uniform scoring criteria in immunohistochemical expression, it is difficult to make clear comparisons among the existing literature for expression of EMT markers that may be involved in oral malignant progression. There are often differences in quantification of amount of staining expression and intensity. Some studies have multiple percentage categories (i.e. absence of staining, less than 10% of cells stained, 10-50% cells stained, and more than 50% cells stained), whereas other studies have only two categories – positive or negative (i.e. positive meaning more than a certain percentage of cells are stained).<sup>55,63</sup> As for staining intensity, some studies have categories to show increasing intensity, where others do not assess for intensity.<sup>42,55,63,65</sup> There are also methods that combine scoring intensity and percentage

stained.<sup>57,58,60</sup> However, in addition to causing challenges to the comparison of results, the semiquantitative methods used may not best represent biological data. Quantitative digital analysis is needed for robust comparisons.

As EMT is a complex biological process, studies must evaluate multiple EMT markers simultaneously to better understand how EMT plays a role in malignant progression. In addition, to understand the complexity of this process, future research should study EMT through single cells using single-cell imaging, lineage tracing, and analysis of gene expression, genetics, and epigenetics.<sup>14</sup> The development of mathematical models can also help outline this complex mechanism.<sup>14</sup>

There are many studies showing the altered expression of E-cadherin and beta-catenin from NOM, OED, to OSCC, but there is a lack of longitudinal research on the role of these proteins as predictors in malignant progression, especially in early malignant progression.<sup>52,54,64,65,69,70,55–61,63</sup> Being able to identify lesions at a high risk of progressing can facilitate early management. The author's (I.Y.) thesis is a pilot study that explored the expression of E-cadherin and beta-catenin in OED to determine whether the expression pattern of these proteins predict malignant progression.<sup>53</sup>

## CONCLUSION

Oral cancer continues to be highly prevalent with head and neck cancer being one of the most common cancers in the world. Identifying oral lesions at a high risk of transforming into cancer may help with early intervention and hopefully reduce the rates of oral cancer or at least improve patient survival rates. Histological diagnosis of dysplasia is the main approach in assessing a lesion's risk of becoming cancer, but there may be interobserver and intraobserver

variability resulting in inaccurate diagnosis and risk assessment. Molecular markers of EMT that are involved in embryogenesis, tissue healing, and cancer development may aid in lesion risk assessment. EMT markers that serve as potential prognostic factors of oral cancer include TWIST, vimentin, and N-cadherin. The EMT markers E-cadherin and beta-catenin may play a role in early malignant progression through the Wnt pathway – a regulatory pathway often involved in disease. Dependent on the loss of E-cadherin and the activation of the Wnt pathway, there may be inhibition of tumour progression, early tumour progression, or late-stage tumour progression. Altered expression levels of E-cadherin and beta-catenin from NOM, OED, to OSCC have been shown in immunohistochemical analysis. However, future research should focus on the longitudinal role of these proteins and use a combination of additional EMT markers in predicting early malignant progression.

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## **CONFLICTS OF INTEREST**

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## **PRACTICE RELEVANCE**

- Increase understanding of the complex biological mechanism epithelial-mesenchymal transition (EMT) and its relationship to oral cancer and potentially oral epithelial dysplasia
- Understand the role of the molecular markers of EMT, specifically E-cadherin and beta-catenin, in oral malignant progression
- Provide directions for future research in the area of EMT and oral dysplasia to guide lesion risk assessment and clinical management

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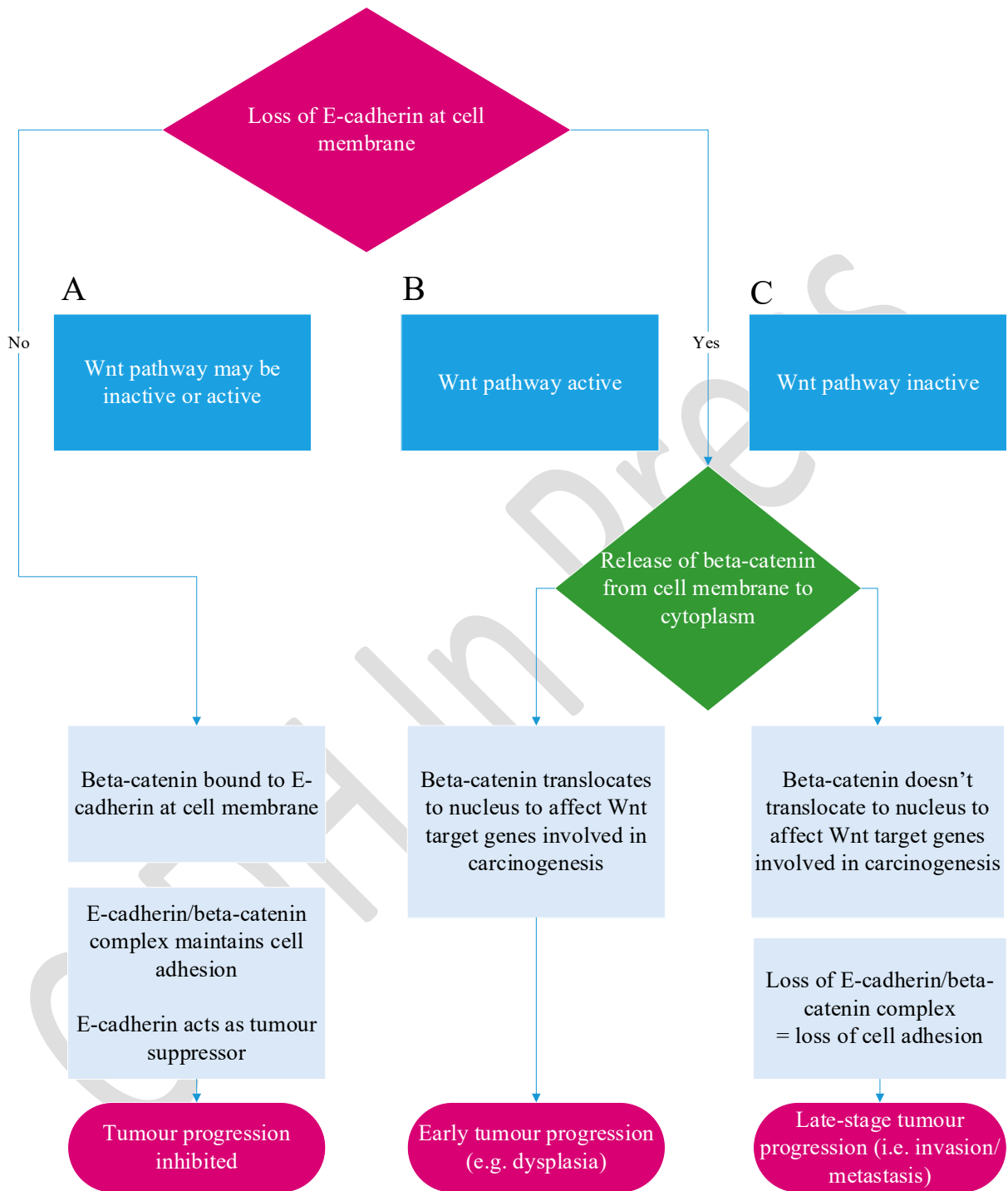
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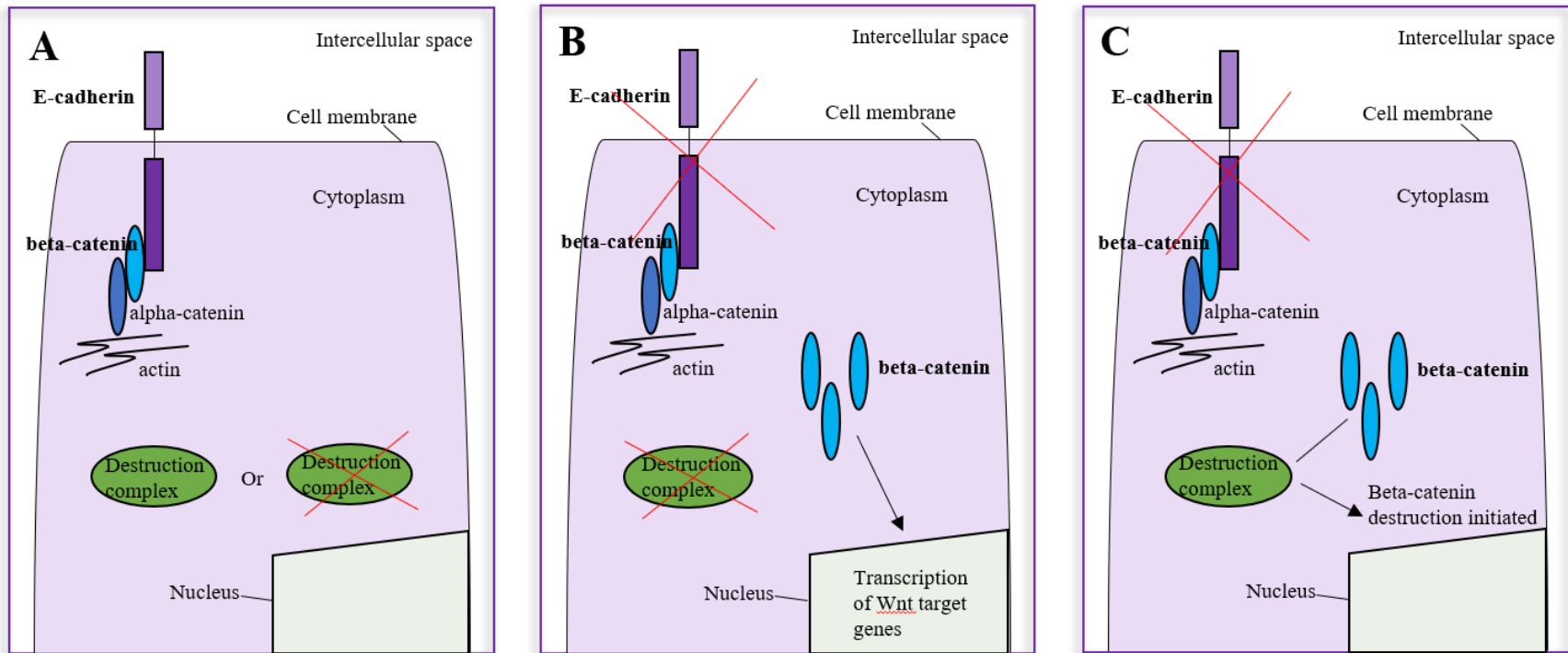
## FIGURES



**Figure 1 E-cadherin, beta-catenin, and the Wnt pathway in malignant progression.**

(A) The presence of E-cadherin at the cell membrane results in the inhibition of tumour progression. (B) The loss of E-cadherin at the cell membrane while the Wnt pathway is active leads to early tumour progression, such as in dysplasia. (C) The loss of E-cadherin at the cell membrane when the Wnt pathway is inactive contributes to the later stages of tumour progression (i.e. invasion and metastasis)

Adapted from Yim, 2022.<sup>53</sup>



**Figure 2 E-cadherin, beta-catenin, and the Wnt pathway in malignant progression in the cell.**

(A) The presence of E-cadherin at the cell membrane results in the inhibition of tumour progression. (B) The loss of E-cadherin at the cell membrane while the Wnt pathway is active leads to early tumour progression, such as in dysplasia. (C) The loss of E-cadherin at the cell membrane when the Wnt pathway is inactive contributes to the later stages of tumour progression (i.e. invasion and metastasis).

Adapted from Yim, 2022.<sup>53</sup>

## TABLES

**Table 1 Expression patterns of E-cadherin in normal oral mucosa (NOM), oral epithelial dysplasia (OED), and oral squamous cell carcinoma (OSCC)**

		NOM	OED	OSCC
<b>E-cadherin expression</b> <sup>52,54,70,55</sup> -61,69	<b>Cell membrane</b>	High	Decreased <sup>a</sup> (except Lopes et al.)	Decreased <sup>ab</sup> (except Lopes et al.)
	<b>Cytoplasm</b>	None (Kaur et al. indicate occasional expression)	None (except Kyrodimou et al.)	Increased <sup>ab</sup>
	<b>Nucleus</b>	None	None	None

<sup>a</sup>compared to NOM

<sup>b</sup>compared to OED

E-cadherin expression in the nucleus has not been commonly reported in oral tissue.

Adapted from Yim, 2022.<sup>53</sup>

**Table 2 Expression patterns of beta-catenin in normal oral mucosa (NOM), oral epithelial dysplasia (OED), and oral squamous cell carcinoma (OSCC)**

		<b>NOM</b>	<b>OED</b>	<b>OSCC</b>
<b>Beta-catenin expression</b> <sup>42,52,54,58,61,63-66</sup>	<b>Cell membrane</b>	High	Decreased <sup>a</sup>	Decreased <sup>a</sup>
	<b>Cytoplasm</b>	None (Kaur et al. and Ishida et al. indicate minimal expression)	Increased <sup>a</sup>	Increased <sup>a</sup> (Mixed results when comparing expression in OSCC to OED)
	<b>Nucleus</b>	None (Kaur et al. indicate minimal expression)	Increased <sup>a</sup> (Especially in severe OED – Chaw et al., Reyes et al., and Lo Muzio et al.)	Increased <sup>a</sup> (Mixed results when comparing expression between OSCC and OED)

<sup>a</sup>compared to NOM

Adapted from Yim, 2022.<sup>53</sup>