

# THE ROLE OF FOXC2 IN CANCER

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Degree in Biochemistry. Universitat Autònoma de Barcelona, 2015. Tutor: Emili Itarte Fresquet.

## INTRODUCTION

The aim of this review is to understand the mechanisms involved in the function of FOXC2 in cancer. The methodology used is based on the revision of scientific literature found in different databases, such as PubMed and ScienceDirect. FOXC2 is a transcription factor with important functions during development of various embryonic organs and tissues because it regulates temporal expression of genes. But recent studies have shown that FOXC2 is also essential in the progression of the tumor because of its expression in tumor cells and in endothelial cells. The nuclear localization of FOXC2 have been correlated with aggressive characteristics during cancer.

## FOXC2

The gene of FOXC2 encodes a protein of 2,2Kb and is characterized by the forkhead box, which is a DNA binding domain.

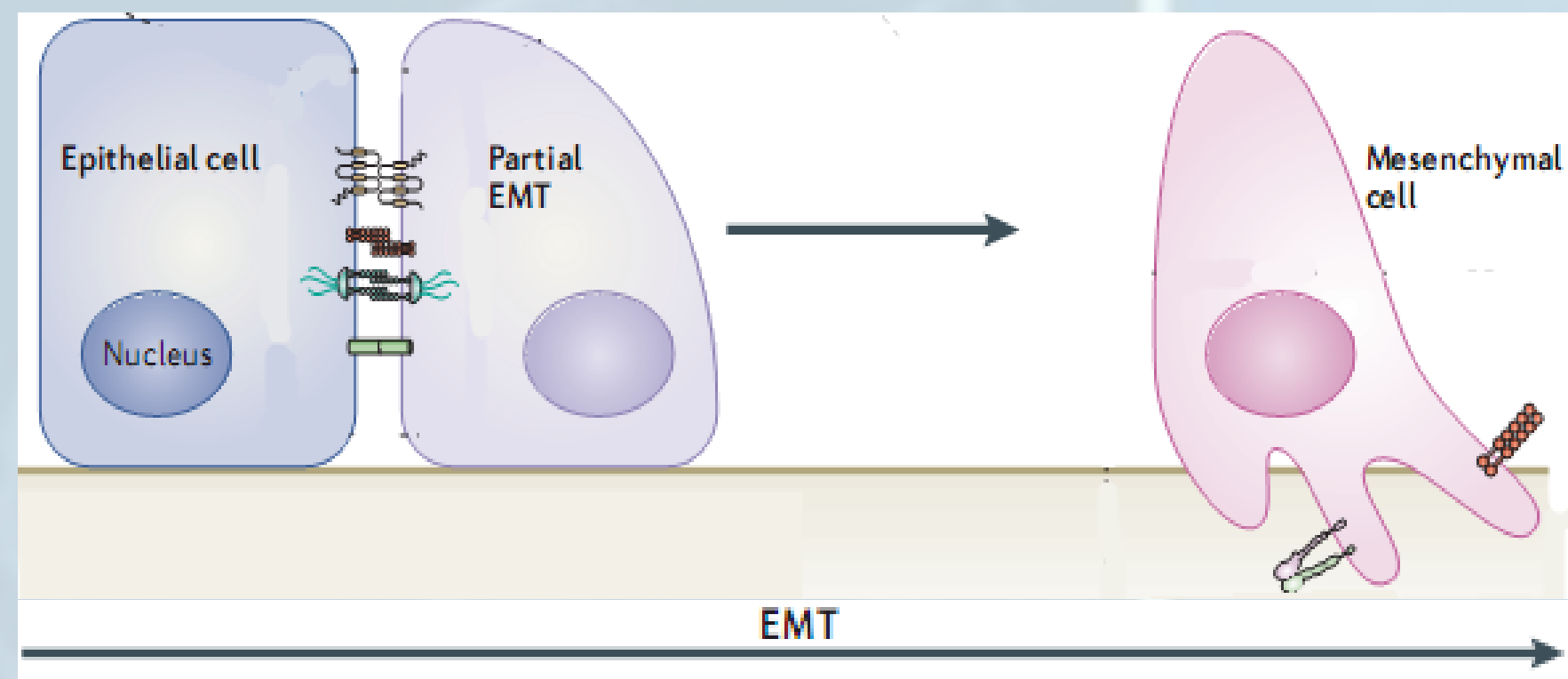
The basic mechanism to act as a transcription factor consists on the highly conserved forkhead DNA-binding domain (FHD) which binds to forkhead response elements (FHREs) in promoter region of target genes.

Furthermore, FOXC2 has different domains that are susceptible to be modified by various enzymes.

## EMT

The epithelial-mesenchymal transition (EMT) consists on the loss of epithelial characteristics and the acquisition of migratory behavior. The EMT during cancer is an important step to benign tumor cells, because leads the cells to acquire the capacity to infiltrate and to be more invasive.

There are important differences between mesenchymal and epithelial cells, as it is shown in figure 1. Those differences are regulated by transcription factors, such as FOXC2.



**Figure 1.** Cellular events during epithelial-mesenchymal transition (EMT). Figure modified from Lamouille et al, 2014.

On the other hand, those changes that occur in epithelial cells, are also present in endothelial cells and are classified as the endothelial-mesenchymal-transition (EndMT).

EndMT involves the endothelial cells from blood and lymphatic vessels. The process consists on an increase in vascular permeability and migratory characteristics which are necessary to lead the newly forming vessel into adjacent tumor.

## FOXC2 - CANCER CELLS

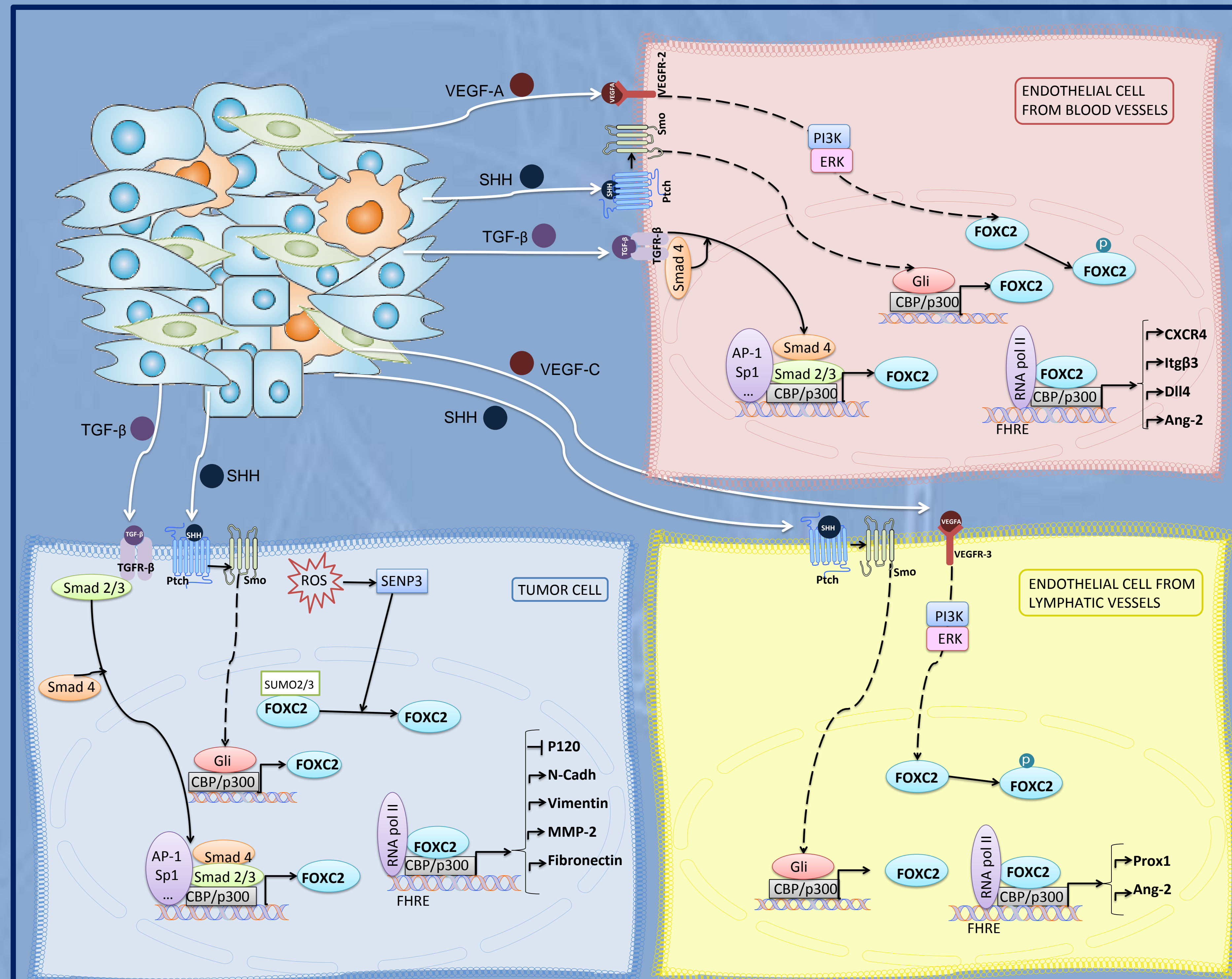
During tumor growth, cancer and stromal cells induce the transcription of FOXC2 in order to acquire the mesenchymal phenotype. The growth factor- $\beta$  (TGF- $\beta$ ) and the Sonic Hedgehog (SHH) are secreted by tumor and stromal cells and promote the transcription of FOXC2, which regulates the expression of different genes involved in the EMT. The transcription factor is stabilized in the nucleus by a specific protease, SENP3, as it is shown in figure 2. FOXC2 suppresses the transcription of p120 but promotes other target genes like N-cadherin, vimentin, fibronectin and MMP-2.

- Suppression of p120 catenin (a regulator of E-cadherin) and upregulation of N-cadherin in order to loose cell-cell adhesion.

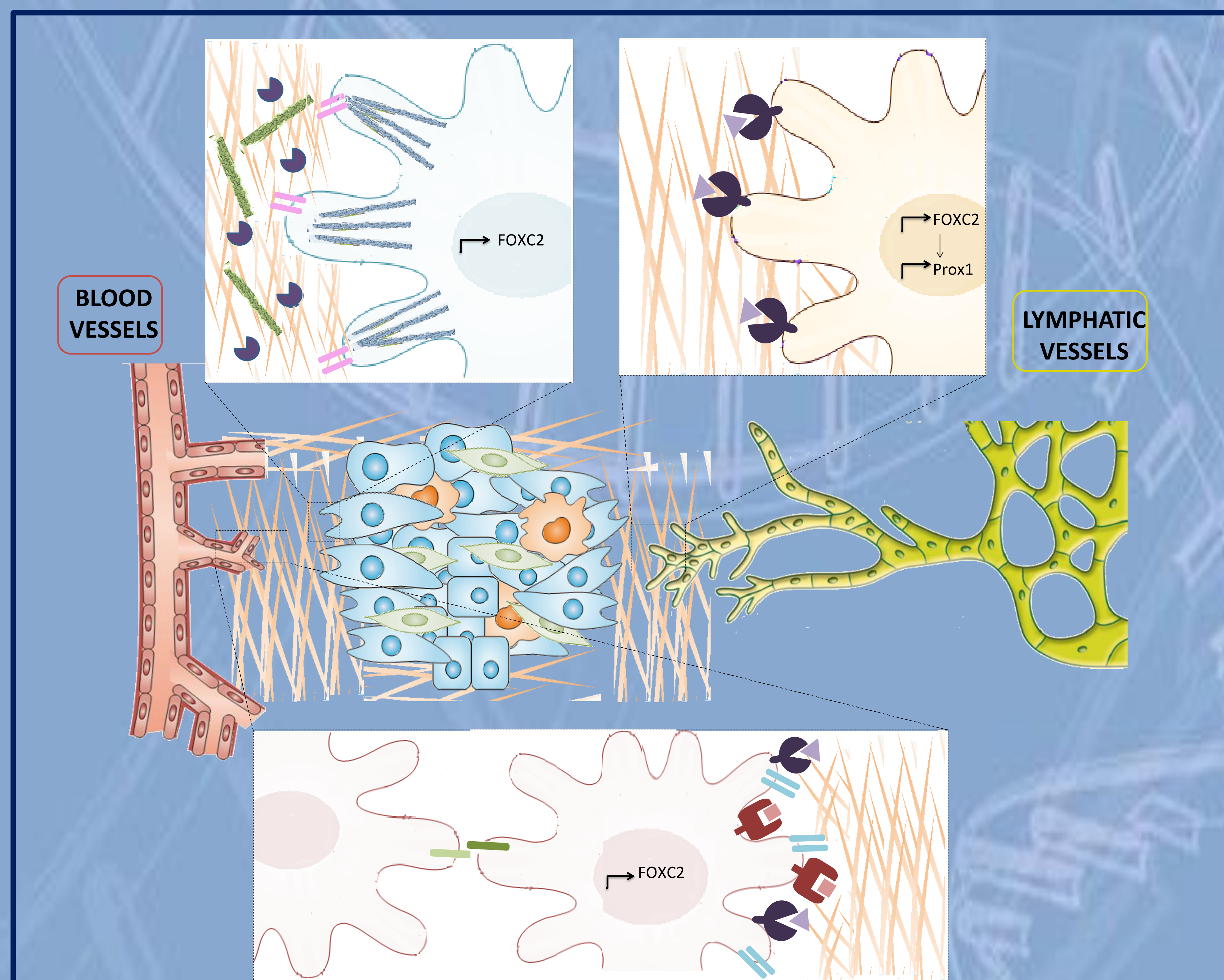
- Vimentin forms intermediate filaments on the surface of cancer cells and regulates focal adhesion and motility.

- It is a large adhesive glycoprotein that is deposited by tumors in the ECM promoting the loss of tissue architecture.

- Metalloproteinase-2 is involved in the breakdown of ECM.



**Figure 2.** The molecular mechanisms involved in the activation and regulation of FOXC2. In blue is represented the tumor cell, in red the endothelial cell from blood vessels and in yellow the endothelial cell from lymphatic vessels.



**Figure 3.** The target genes activated by FOXC2 in tumor cell and endothelial cells from blood and lymphatic vessels during EMT and EndMT.

## Bibliography

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## FOXC2 - ENDOTHELIAL CELLS

### Angiogenesis

Angiogenesis is a crucial contributor to cell invasion and metastasis because blood vessels supplies oxygen and nutrients to the tumor. It involves cellular and morphological changes in endothelial cells driven by transcription factors, such as FOXC2.

During angiogenesis FOXC2 can be induced by different signals. The major angiogenic factor is the vascular endothelial growth factor (VEGF-A), which is produced by tumor and stromal cells and acts through its receptor VEGFR-2. The role of VEGF-A in FOXC-2 consists in stabilizing the transcription factor. However, TGF- $\beta$  and SHH directly induces FOXC2.

The target genes promoted by FOXC2 in blood vessels are CXCR4, Integrin  $\beta$ 3, Dll4 and Ang-2:

- CXCR4: It is a chemokine that regulates the directional migration of endothelial cells to tumor cells because tumor cells secrete its ligand, CXCL12.

- Integrin  $\beta$ 3: Interacts with matrix components inducing cell adhesion and migration.

- Dll4: It is involved in the growing sprout of the vessels when it binds to Notch on the adjacent endothelial cell.

- Ang-2: Ang-2 induces maturation and remodeling of the blood vessels. It binds to the Tie2 receptor expressed in the endothelial cells.

### Lymphangiogenesis

Lymphangiogenesis is the mechanism by which lymphatic vessels undergo dynamic changes in order to facilitate tumor invasion and metastasis.

As in angiogenesis, VEGF is an important factor, but in lymphatic vessels the ligand implicated is VEGF-C which binds to its receptor VEGFR-3 and stabilizes FOXC2. The main inducer of this transcription factor during lymphangiogenesis is SHH.

FOXC2 directly induces the transcription of Ang-2 and Prox1 in endothelial cells from lymphatic vessels:

- Ang-2: Ang-2 binds to its receptor Tie-2 at endothelial cells and promotes maturation of lymphatic vessels.

- Prox1: Prox1 is a transcription factor specific for lymphatic vessels and is required during migration of lymphatic endothelial cells.

## CONCLUSIONS

- ❖ FOXC2 has important roles inducing EMT in cancer cells but also inducing EndMT in endothelial cells from blood and lymphatic vessels.

- ❖ The molecular mechanisms involved in the induction and regulation of FOXC2 are highly complex and not well known.

- ❖ Other important pathways may be involved in the induction and stabilization of the transcription factor. Experiments so as to better identify the molecular pathways related to induction of FOXC2 may contribute to better knowledge.

- ❖ All the mechanisms described occurs in normal situations, when the tumor grows and consequently appear zones with low percentage of oxygen. Maybe a driver mutation in FOXC2 would accelerate this process.

- ❖ Further investigation is needed to know the molecular mechanisms by which FOXC2 acts and its target genes.