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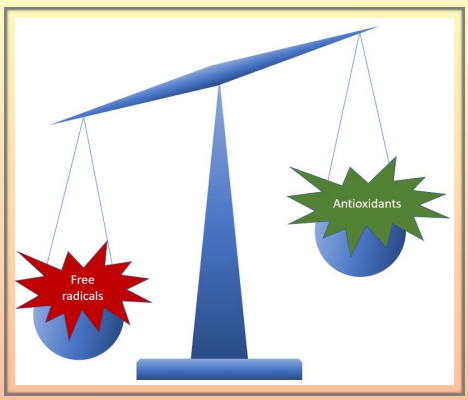
# Melatonin : The Smart Protector of the Placenta!

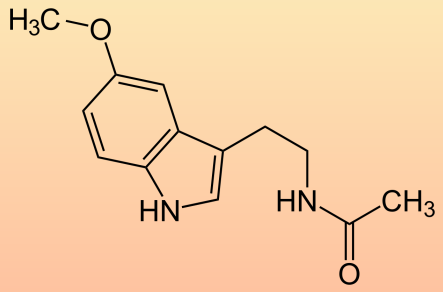
*The pregnancy toxicology laboratory of Dr. Cathy Vaillancourt at Centre INRS-Institut Armand-Frappier aims to identify the mechanisms of action of melatonin in the placenta. An article by Fatma Kharrat, MSc student in the laboratory of Dr. Cathy Vaillancourt.*

Pregnancy is a critical stage of life, during which many physiological processes are modified. It is also a state of increasing oxidative stress (Myatt et al., 2004). Long described as the regulator of circadian rhythms (Zhdanova et al., 2005), melatonin is also increasingly mentioned as a cell-protective molecule. Indeed, it has different properties allowing it to exert its strong antioxidant power (Galano et al., 2013). Melatonin is more effective in fighting free radicals than other well-known natural or chemically synthesized antioxidants (Martin et al., 2000, Reiter et al., 2009). Melatonin has a unique

**Oxidative stress** : *Occurs when the production of Reactive Oxygen Species (metabolites produced after oxygen use or ROS) exceeds the intrinsic antioxidant defense, thereby causing molecular damage leading to apoptotic cell death.*



**Melatonin:** *(N-acetyl-5- methoxytryptamin): member of the indolamine family, molecules having an amine group linked to an indole ring. It is synthesized from serotonin.*



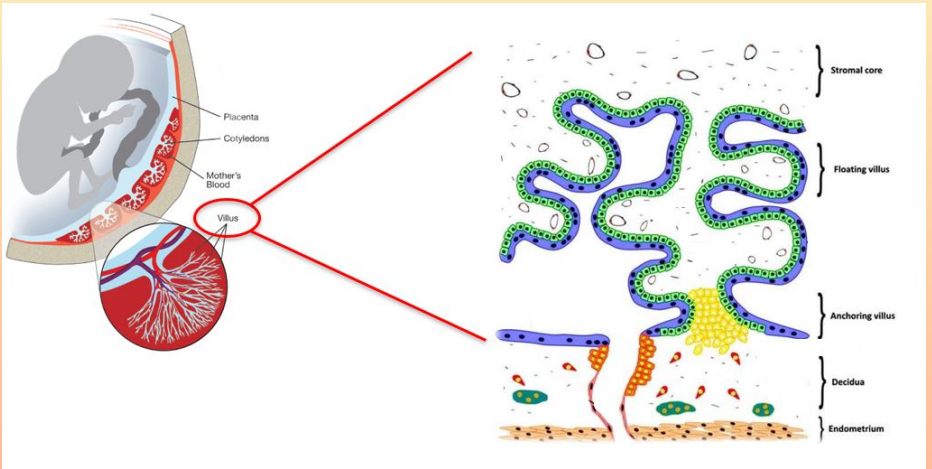

feature: **ubiquitous distribution**. Thanks to its **amphiphilic** properties, both hydrophilic and lipophilic, there are no morphophysiological barriers for this molecule! It can transfer easily itself between cellular compartments and has access to major Reactive oxygen Species (ROS) production sites such as mitochondria, where melatonin is also known to be produced.

Interestingly, melatonin metabolites are also ROS scavengers, because this molecule is the progenitor of multiple of radical neutralizers operating in a cascade to prevent ROS-induced cellular damage (Tan et al., 2002; Sagrillo-Fagundes et al., 2014). In this way, melatonin acts **directly** on free radicals, but it can also act **indirectly**, via activation of its receptors which stimulate antioxidant enzyme expression (Richter et al., 2009; Rodriguez et al., 2004).

The team of Dr. Vaillancourt, is interested in elucidating melatonin's function within the placenta. Her team discovered that melatonin is produced by the trophoblastic cells of the placenta, which also express its MT1 and MT2 receptors. Melatonin acts in an autocrine, intracrine and paracrine manner in this organ (Lanoix et al., 2008; Sagrillo-Fagundes et al., 2014). In 1991, Kivela et al. demonstrated an increase in melatonin levels in the maternal blood during pregnancy. The work of Dr. Vaillancourt's team suggests that this increase is due to placental production of melatonin (Lanoix et al., 2008). In a situation of oxidative stress, generated by hypoxia / reoxygenation, melatonin protects placental cells against damage. It decreases ROS levels by neutralizing them and increases the expression and the activity of **antioxidant** enzymes, demonstrating its antioxidant action at the placenta level.

In the presence of oxidative stress, melatonin also protects the placental trophoblasts against the induction of apoptosis (programmed cell death) via the mitochondrial pathway. Indeed, Dr. Vaillancourt's team has shown that melatonin

**Trophoblastic cell:** *Main cell constituting the chorionic villus, the structural and functional unit of the placenta. It has a nurturing, metabolic and endocrine role, and also produces melatonin. Adapted from Sagrillo-Fagundes et al., 2014.*



maintains the oxidative balance between pro and antioxidant species, preventing cell death by apoptosis (Lanoix et al., 2013).

healthy cells. We have shown a pro-apoptotic action of this indolamine (Lanoix et al., 2012).

Current work in our laboratory aims to elucidate the mechanism by which melatonin exerts a pro-oxidative effect in tumor cells. Our preliminary results show that melatonin increases the levels of ROS in BeWo cells. It also increases the expression of Xanthine Oxidase, a pro-oxidant enzyme considered as the major generator of ROS. In addition, melatonin increases the level of antioxidant enzymes (catalase, glutathione peroxidase, superoxide dismutases ...). The treatment of BeWo cells with melatonin also increases lipid peroxidation and protein carbonylation, considered as the major hallmarks of oxidative stress damage.

How can this smart molecule exert completely opposite effects according to the type of cell it encounters? Our work in progress will answer this question and will allow a better understanding regarding the duality of action of melatonin in healthy versus tumoral cells.

**Fatma Kharrat**

*MSc student in the Dr Vaillancourt's laborarory.*

## Work in progress in the Dr. Vaillancourt's laboratory

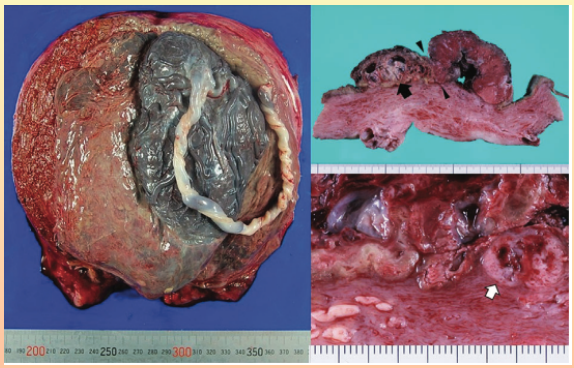
Melatonin a "smart killer" ...

The antitumor action of melatonin has been shown in different cancer cell types (Mediavilla et al., 2010). In liver cancer (Zha et al., 2011), renal cancer (Um et al., 2010), and melanomas (Kim et al., 2014), melatonin has a **pro-apoptotic** effect, the opposite of action it exerts in healthy cells, which is fascinating!

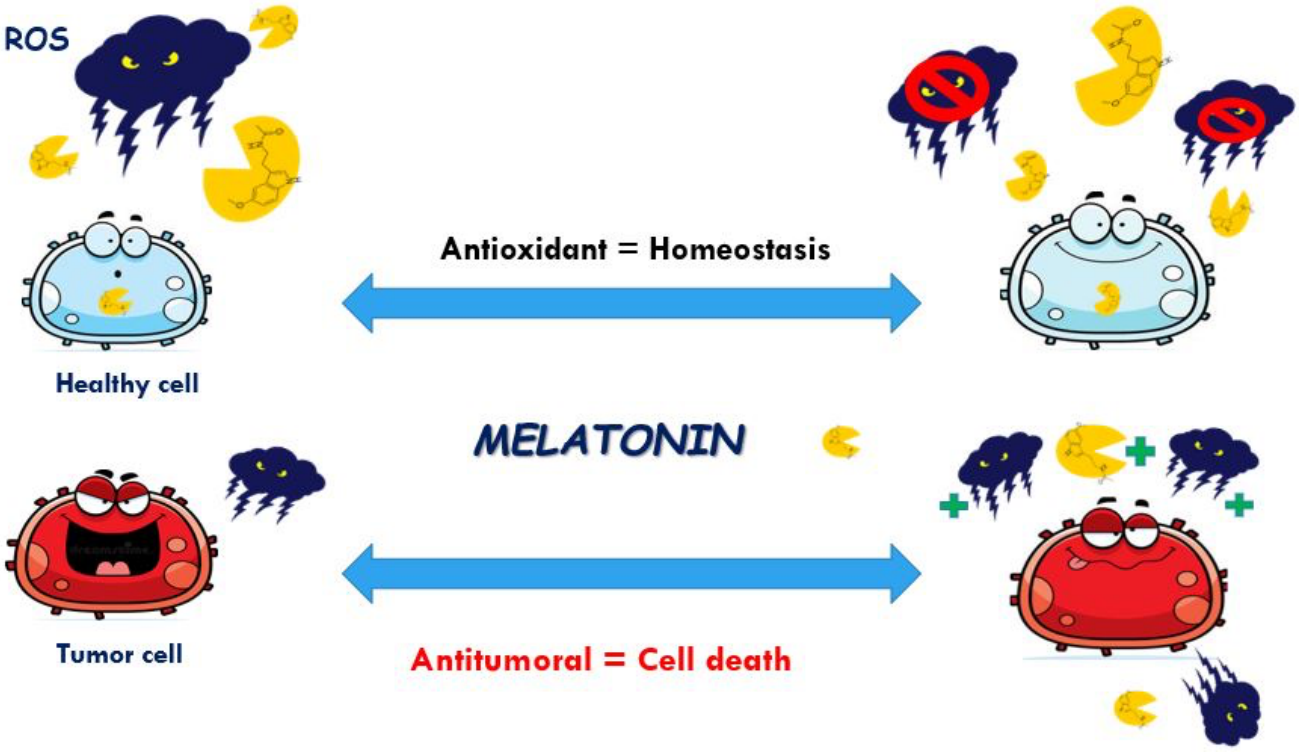
Indeed, it can be **pro-oxidative**, by inducing oxidative stress in cancer cells, leading them do death by apoptosis (Casado-Zapico et al., 2010, Dziegiel et al., 2003). However, the action of melatonin has never been studied in placental tumor cells.

The Dr. Vaillancourt's laboratory is working on elucidating the antitumoral action of melatonin in the placenta using a cell model of placental choriocarcinoma, **the BeWo cell line.**

BeWo cells, as healthy placental trophoblasts, synthesize melatonin and express its receptors (Lanoix et al., 2006, 2008; Soliman et al., 2015). So far, our team has shown that these cells react differently to melatonin compared to



**Placental choriocarcinoma** *is the result of the transformation of healthy trophoblasts into malignant tumors. It affects* **1 in 40,000** *women and is usually treated with chemotherapy. From Maeda et al., 2018; Ganapathi et al., 2010; Kaplan, C.G. et al., 2009*




## Coming events

- 13th edition of 24h of science: the event will take place on May 10th and 11th, 2019

- The "Pint of science" festival will take place from May 20th to May 22nd, 2019.
https://pintofscience.ca/contact/

- Four students: Laurie Pinel, Laura Girardet, Olivia Smith and Anne-Sophie Pépin and a researcher, Dr. Daniel Cyr, will represent the RQR at the ReproSciences meeting in Toulouse, France, from April 24th to 26th. This meeting is organized by GDR Repro 3606.