

# Table of contents

Abbreviations.....	7
<b>1. Introduction.....</b>	<b>13</b>
<b>1.1 Epigenetics.....</b>	<b>14</b>
<b>1.2 Chromatin organization: .....</b>	<b>16</b>
<b>1.3 Histones modifications: .....</b>	<b>18</b>
1.3.1 Histone acetylation .....	18
1.3.2 Histone methylation.....	19
1.3.3 Other histone modifications .....	21
<b>1.4 DNA modifications .....</b>	<b>21</b>
1.4.1 Cytosine methylation.....	22
1.4.2 The 5mC machinery .....	22
1.4.3 5mC distribution and consequence on gene expression .....	23
1.4.4 Methylome mapping technologies .....	24
1.4.5 Pathological implications of 5mC .....	26
1.4.6 Cytosine hydroxymethylation .....	27
1.4.7 The 5hmC machinery .....	29
1.4.8 5hmC distribution and consequence on gene expression .....	29
1.4.9 Hydroxymethylome mapping technologies.....	32
1.4.10 Pathological implications of 5hmC .....	32
1.4.11 Other covalent DNA modification. ....	34
1.4.12 Methylation of adenine.....	34
<b>1.5 Crosstalks in Epigenetics .....</b>	<b>36</b>
<b>1.6 RNA modifications .....</b>	<b>37</b>
1.6.1 Methylation of adenosine .....	37
1.6.2 m6A machinery .....	39
1.6.3 m6A distribution.....	41
1.6.4 Pathological implications of m6A .....	42
1.6.4.1 m6A in breast cancer.....	43
1.6.5 Other mRNA modifications .....	44
<b>1.7 Breast cancer.....</b>	<b>45</b>
1.7.1 Breast cancer subtypes .....	47
1.7.1.1 Histology-based subtypes.....	47
1.7.1.2 Molecular-based subtypes:.....	47

1.7.2 Immune infiltration in breast cancer.....	49
1.7.3 Breast cancer treatments.....	51
1.7.4 Epigenetics in breast cancer .....	51
<b>1.8 The NF-<math>\kappa</math>B signaling pathway .....</b>	<b>54</b>
1.8.1 The canonical pathway:.....	54
1.8.2 The non-canonical pathway:.....	55
1.8.3 The NF- $\kappa$ B pathway in cancers.....	56
1.8.3.1 Pro-tumorigenic roles of the NF- $\kappa$ B pathway:.....	56
1.8.3.2 Anti-tumorigenic roles of the NF- $\kappa$ B pathway:.....	56
1.8.3.3 NF- $\kappa$ B in breast cancer:.....	57
1.8.4 Therapies targeting the NF- $\kappa$ B pathway .....	57
<b>1.9 The WNT signaling pathway .....</b>	<b>58</b>
1.9.1 The canonical pathway .....	59
1.9.2 The non-canonical pathway.....	60
1.9.3 The WNT pathway in cancers .....	60
1.9.3.1 The WNT pathway in breast cancer:.....	61
1.9.3.2 Implications in immunotherapy.....	61
1.9.4 Therapies targeting the WNT pathway.....	62
<b>2. Aims of this thesis .....</b>	<b>64</b>
<b>3.0. Chapter I: Immunity drives TET1 regulation in cancer through NF-<math>\kappa</math>B. ....</b>	<b>66</b>
<b>3.0.1 Introduction .....</b>	<b>67</b>
<b>3.0.2 Results.....</b>	<b>69</b>
3.0.2.1 TET1 regulation is associated with 5hmC changes in BLBC .....	69
3.0.2.2 In basal-like tumors, high TET1 expression is associated with low levels of immune and defense response markers.....	70
3.0.2.3 TET1 expression is repressed by NF- $\kappa$ B activation.....	70
3.0.2.4 TET1 is repressed through binding of NF- $\kappa$ B to its promoter .....	72
3.0.2.5 TET1 is down-regulated by NF- $\kappa$ B in other cancer types.....	72
<b>3.1 Chapter II: Downregulation of the m6A RNA demethylase FTO promotes EMT-mediated tumor progression and confers sensitivity to Wnt inhibitors .....</b>	<b>74</b>

<b>3.1.1 Introduction .....</b>	<b>75</b>
<b>3.1.2 Results.....</b>	<b>77</b>
3.1.2.1 FTO loss enhances tumor progression.....	77
3.1.2.2 FTO loss elicits an EMT program. ....	77
3.1.2.3 FTO controls Wnt signaling in cancer.....	80
3.1.2.4 FTO-low tumors are sensitive to WNT inhibitor therapy. ....	82
<b>4.0. Discussion.....</b>	<b>84</b>
<b>4.1 Immunity drives TET1 regulation in cancer through NF-<math>\kappa</math>B. ....</b>	<b>85</b>
<b>4.2. Downregulation of the m6A RNA demethylase FTO promotes EMT-mediated tumor progression and confers sensitivity to Wnt inhibitors. ....</b>	<b>90</b>
<b>5.0. Conclusion .....</b>	<b>97</b>
<b>6.0. References.....</b>	<b>99</b>
<b>7.0. Appendix.....</b>	<b>137</b>
<b>7.1. Manuscript I.....</b>	<b>138</b>
<b>7.2. Manuscript II .....</b>	<b>175</b>