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Obesity and Melanoma: Exploring Molecular Links

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ABSTRACT

Obesity is now a major health problem due to its rapidly increasing incidence worldwide and severe consequences. Among many conditions associated with obesity are some cancers including melanoma. Both genetic defects and environmental risk factors are involved in the carcinogenesis of melanoma. Activation of multiple signal pathways such as the PI3K/Akt and MAPK pathways are necessary for the initiation of melanoma. Activation of the MAPK pathway as a result of activating mutations in BRAF is commonly seen in melanoma though it alone is not sufficient to cause malignant transformation of melanocytes. Obesity can result in the activation of many signal pathways including PI3K/Akt, MAPK, and STAT3. The activation of these pathways may have a synergistic effect with the genetic defects thereby increasing the incidence of melanoma. J. Cell. Biochem. 114: 1955–1961, 2013.

KEY WORDS: OBESITY; MELANOMA; PI3K/AKT; MAPK; STAT3

Obesity is now recognized as a major global health problem due to its rapidly increasing incidence worldwide and the conditions with which it is associated. It has been estimated that there were 1.46 billion overweight or obese adults worldwide with body mass index (BMI) equal to or greater than 25 in 2008 [Finucane et al., 2011]. Among them, 205 million men and 297 million women were obese who had BMI equal to or greater than 30. Obesity has been shown to be related to a number of conditions, including some cancers. This is mainly demonstrated by epidemiological studies showing a strong positive correlation between BMI and the incidence of various cancers, including colon, breast, ovarian, prostate, thyroidand melanoma [Calle and Kaaks, 2004; Renehan et al., 2008; Huang and Chen, 2009a; Chen, 2011; Mijovic et al., 2011; Paz-Filho et al., 2011a; Thomas and Freedland, 2011]. The incidence of melanoma has been increasing steadily over the past few decades in most Western countries [Karim-Kos et al., 2008] and obesity has been postulated to be one of the causes for the increased incidence of melanoma [Samanic et al., 2004; Oh et al., 2005; Mantzoros et al., 2007; Dennis et al., 2008; Gogas et al., 2008; Renehan et al., 2008; Shipman, 2011]. Among the explanations proposed for the obesity-melanoma link are increased blood levels of insulin, insulin-like growth factor 1 (IGF-1), leptin, VEGF, interleukin (IL)-6, IL-17, TNF-alpha as well as decreased blood levels of adiponectin [Brandon et al., 2009; Chen and Huang, 2009; Duggan et al., 2010; Gallagher and LeRoith, 2010; Huang et al., 2010; Sharma et al., 2010; Gu et al., 2011; Paz-Filho et al., 2011a].

High serum levels of leptin, a cytokine produced by adipose tissues (adipokine)[Paz-Filho et al., 2011b] have been shown to be associated with an increased melanoma risk [Gogas et al., 2008; Kushiro et al., 2012]. In animal experiments, high-fat diet-induced obesity increased melanoma growth in a xenograft model with increased blood levels of insulin and leptin [Pandey et al., 2012]. However, the biological mechanism(s) linking obesity with melanoma are yet to be established. We propose that obesity-associated activation of multiple signal pathways may play key roles in the development of obesity-associated melanoma. For example, the activation of the phophoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway in obesity could act in a synergistic manner with the activated mitogen-activated protein kinase(MAPK) pathway caused by the mutations of v-Raf murrine sarcoma viral oncogene homolog B1 (BRAF) to promote the carcinogenesis of melanoma and thereby increase the incidence of the disease.

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MULTIPLE GENETIC DEFECTS ARE NECESSARY FOR THE INITIATION OF MELANOMA

Cutaneous melanoma is a highly malignant disease responsible for 80% of all skin cancer deaths although it accounts for only 10% of all skin cancers. It is caused by both genetic defects and environmental factors such as UV exposure [Chin, 2003; Chin et al., 2006; Ghosh and Chin, 2009]. The roles of genetic defects in the carcinogenesis and metastasis have been studied extensively [Kabbarah et al., 2010]. For example defects of BRAF [Davies et al., 2002, 2009; Gopal et al., 2010], NRAS, KIT [Curtin et al., 2006] and ERBB4 [Prickett et al., 2009] in melanoma are well known. Mutation of NRAS is also common in melanoma, with frequencies estimated at50–60% [Demunter et al., 2001; Davies et al., 2002; Pollock et al., 2003]. These mutations regulate down-stream pathways and target proteins such as LKB1 to contribute to the development of cancer [Zheng et al., 2009]. Activation of the PI3K/Akt pathway in melanoma can occur by activation of *PI3KCA* (the gene encoding the p110α catalytic subunit of PI3K) or *Akt* gene itself, or lost expression of *PTEN* (phosphate and tensin homolog deleted on chromosome 10) (Fig 1). It has been shown that the *Akt3* mutation is presentin 43–60% of non-familial melanomas [Stahl et al., 2004]. Other gene mutations have been identified that appear to play important roles in melanoma. For example, Wei et al. [2011] identified *TRRAP*, *GRIN2A*, and *PLCB4* as possible candidates in the study of exome sequencing. Knockout of mutated *TRRAP* in melanoma cells increased apoptosis while GRIN2A protein belongs to glutamate pathway which is known to have therapeutic implications [Rzeski et al., 2001; Stepulak et al., 2005, 2007, 2011]. PLCB4protein has been shown to be involved in the regulation of the protein kinase C pathway [Pin et al., 1995].

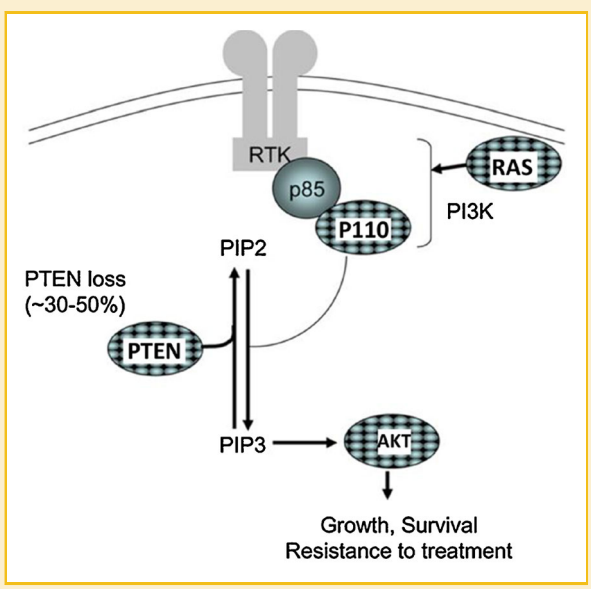

Figure 1. The PI3K/Akt signalling pathway. In the cytoplasm, PI3K (complex of p85 and catalytic p110) is activated downstream of receptor tyrosine kinases (RTKs) and G protein coupled receptors (not shown). The RAS proto-oncogene also activates PI3K along with the MARK pathway. PI3K phosphorylates PIP2 to generate PIP3, which leads to Akt activation and enhance cell growth, proliferation, and survival. PTEN negatively regulates Akt activation through dephosphorylation of PIP3.

The molecular defects in melanoma are heterogenic [O'Hagan et al., 2003; Kabbarah and Chin, 2005]. For example, in UV-related melanoma, $p16^{INK4A}$ inactivation has been associated with increased cdk6, while in melanoma caused by non-UV agents there is no increase in cdk6 [Kannan et al., 2003]. Under UV, *CDKN2a* is damaged, resulting in abnormalities of two pathways $p16^{INK4A}$/Rb and $p14^{ARF}$ [Kannan et al., 2003; Sharpless and Chin, 2003]. In a mouse model, knockout of $p16^{INK4A}$ or $p14^{ARF}$ synergies the effect of activation of *RAS* [Sharpless et al., 2003]. Thus $p16^{INK4A}$and $p14^{ARF}$ proteins can co-operatively suppress the development of melanoma.

Evidence implies that multiple genetic defects are necessary for the initiation of melanoma. For example, activation of MAPK resulting from *BRAF* mutations was shown not sufficient to cause the cancer by itself. $BRAF^{V600E}$ was found in 82% nevi, indicating *BRAF* mutation is not sufficient for the development of melanoma [Pollock et al., 2003]. This position is supported by demonstrating study in a skin tissue model that BRAF mutation alone was insufficient to cause melanoma [Chudnovsky et al., 2005]. It has also been shown that *PTEN* deficiency and *RAS* activation has co-operatively increased metastasis [Nogueira et al., 2010; Tanaka et al., 2011]. This result suggests that multiple genetic defects are necessary for the initiation of melanoma.

SYNERGISTIC EFFECT OF MULTIPLE SIGNALLING PATHWAYS IN THE INITIATION OF MELANOMA

Multiple signal pathways have been shown to play key roles in carcinogenesis, metastasis and drug resistance [Chen, 2008, 2010; Chen et al., 2010]. Aberrant activation of survival signaling pathways has been shown to be important in melanoma development, progression, and resistance to treatment [Hersey and Zhang, 2001; Ruth et al., 2006; Liang et al., 2011]. Of particular importance, constitutive activation of the MAPK pathway has been shown to be present in over 80% of primary melanomas and up to 70% of spontaneous melanomas have increased PI3K activity [Becker et al., 2006; Gogas et al., 2008]. Activation of these signal pathways can increase cell proliferation, motility, and decrease apoptosis [Chen and McMillan, 2008; Hanahan and Weinberg, 2011].

PI3K/AKT PATHWAY IN THE CARCINOGENESIS OF MELANOMA

The PI3K/Akt pathway plays important roles in many cancers including melanoma [Zhao, 2008]. PI3K is frequently activated in melanoma via loss of PTEN, a lipid and protein phosphatase that antagonises PI3K signaling. In between 50% and 91% of primary melanomas, PTEN protein expression is decreased or absent; this is a result of the loss of heterozygosity at the *PTEN* locus (10% and 50%) [Ming and He, 2009; Paraiso et al., 2011]. In addition to PTEN other major elements of the PI3K pathway have been found to be mutated or amplified in melanomas [Chudnovsky et al., 2005; Madhunapantula and Robertson, 2009]. For example, AKT3 expression is increased in 53% of primary melanomas and 67% of metastatic melanomas. The p110α catalytic subunit of PI3K is activated by mutation in 5% of melanomas. Moreover, activating mutations in receptor tyrosine kinases such as c-KIT, EGFR, and PDGFR also contribute to activation of PI3K in a small proportion of melanomas [Rakosy et al., 2007; Suzuki et al., 2007; Akslen et al., 2008].

Under physiological conditions PI3K signaling begins with the engagement of growth factors to receptor tyrosine kinases [Zhao, 2008]. PI3K is then recruited to plasma membrane-anchored receptors, and activated and phosphorylates the lipid substrate PIP2 to generate PIP3. The downstream AKT serine-threonine kinase binds PIP3, where it is activated by two phosphorylation events and then phosphorylates many substrates to trigger a complex signal cascade that regulates growth, proliferation, survival and motility. Activated Akt phosphorylates up to 100 substrates to regulate a variety of cellular functions such as proliferation and apoptosis [Courtney et al., 2010; Dong et al., 2011]. A major down-stream target of PI3K/Akt is mTOR which plays a critical in carcinogenesis through control of cell proliferation, survival, motility, protein synthesis and transcription, and cellular metabolism [Pollak, 2012]. mTOR regulates p70S6K to increase protein translation which is necessary for cancer cell growth. mTOR also phosphorylates 4EBP so that 4EBP cannot bind and block transcriptional effect of eIF-4E, resulting in increased transcription of eIF-4E targeting genes. The important role of mTOR in melanoma carcinogenesis has been demonstrated by several studies [Aziz et al., 2010; Populo et al., 2012; Sznol et al., 2012].

MAPK PATHWAY IN THE CARCINOGENESIS OF MELANOMA

There are several MAPK pathways identified as being involved in carcinogenesis [Chen et al., 2011a,b]. Among them, the RAF/MEK/ERK pathway is constitutively activated in over 80% of primary and virtually all metastatic melanomas. Aberrant activation of the RAF/MEK/ERK pathway in melanoma stems primarily from activating mutations of BRAF with the most common mutation being a glutamic acid for valine substitution at position 600 ($BRAF^{V600E}$), which occurs in ~50-60% of melanomas [Davies et al., 2002; Smalley, 2010]. Among the three RAF isoforms, ARAF, BRAF and CRAF, BRAF is the main one which mediates RAS and MEK signaling under physiological conditions as it is the most sensitive to RAS stimulation [Ibrahim and Haluska, 2009]. In addition, activating mutations in N-*RAS*, *H-RAS*, *c-Kit*, *ERBB4*, or the G-protein α-subunit GNAQ are responsible for constitutive activation of the MEK/ERK pathway in subsets of melanomas [Curtin et al., 2005; Sensi et al., 2006; Dhomen and Marais, 2009; Prickett et al., 2009; Van Raamsdonk et al., 2009]. Early studies defining the role of MEK/ERK signaling in cycle progression led to a perception that the ERK pathway is primarily involved in regulation of cell growth [Lavoie et al., 1996]. However, increasing evidence indicates that this pathway also contributes to cell survival [Balmanno, 2009]. Moreover, activation of the pathway plays a role in melanoma-associated angiogenesis and evasion of immune surveillance [Sharma et al., 2005; Sumimoto et al., 2006].

It has been shown that activation of the MAPK pathway itself is not sufficient for the carcinogenesis of melanoma [Babchia et al., 2009]. However, an additional abnormality of another signal pathway is sufficient to cause melanoma. This is perhaps best demonstrated by studies showing cooperative interactions between $BRAF^{V600E}$ and Akt activation in melanoma initiation and development [Cheung et al., 2008; Ibrahim and Haluska, 2009; Nogueira et al. 2010; Karreth et al., 2011]. Co-expression of BRAF and Akt3 in melanocytes resulted in malignant transformation of the cells [Cheung et al., 2008]. Decreased p53 pathway has also been demonstrated to synergise the effect of BRAF to initiate melanoma in a zebrafish model [Patton et al., 2005].

ACTIVATION OF MULTIPLE SIGNALLING PATHWAYS IN OBESITY

Superfluous adipose tissues as a result of obesity could be a source to produce extracellular factors that stimulate activation of several pathways includingPI3K/Akt, MEK/ERK and stat3 [Chen, 2012a,b]. A number of biological changes associated with obesity have been identified as cancer risk factors, including increased insulin and insulin-like growth factor (IGF) activity, changes in the production of adipokines including increased circulating leptin and decreased serum levels of adiponectin, elevated levels of IL-6 and IL-17, and obesity-associated hypoxia and inflammation [Huang and Chen, 2009b; Gislette and Chen, 2010; Chen, 2011].

The serum levels of insulin have been shown to be positively correlated with increasing BMI. A prolonged increase in circulating insulin causes reductions in the production of IGF binding protein (IGFBP)-1 and IGFBP-2, which normally bind to IGF-I and inhibit its activity, that in turn results in increases in free IGF-1 levels [Chen, 2011]. Binding of insulin and IGF-1 to their respective receptors on the cell surface leads to activation of both the MAPK and PI3K/Akt pathways [Huang and Chen, 2009a,b; Chen, 2011].

More than 50 adipokines have been identified to date. Among them, leptin and adiponectin are the most abundant and most extensively studied in relation to cancer. Leptin is closely related to insulin, in that the latter acts as a positive feedback to activate leptin gene expression [Paz-Filho et al., 2011a,b]. Through binding to the long form of its receptors (LRb), it activates the PI3K/Akt and MAPK pathways. The circulating levels of adiponectin are negatively correlated with BMI. The decreased levels of this adipokine contribute to activation of PI3K/Akt by multiple mechanisms such as inhibition of AMP-activated protein kinase (AMPK) and increased production of leptin and cytokines including IL-6 and IL-17 [Huang and Chen, 2009a,b]. The latter has been shown to activate the PI3K/Akt pathway [Gislette and Chen, 2010].

Another important survival pathway activated in obesity is STAT3 [Chen, 2011] which can be stimulated by IL-6, leptin. The downstream target of PI3K/Akt and MAPK can also activate STAT3. Activated STAT3 in turn regulates transcription of many genes that can promote carcinogenesis. For example, it has been demonstrated that IL-6/STAT3 pathway is critical in the development ofobesity-associated livercancer [Park et al., 2010]. Therefore, multiple signal pathways including PI3K/Akt, MAPK and STAT3 are activated in obesity and these pathways have the ability to contribute to the development of some cancers.

COMBINATORIAL EFFECTS OF OBESITY AND GENETIC MUTATIONS IN OBESITY-ASSOCIATEDMELANOMA

It seems reasonable to assume that activation of multiple signal pathways in obesity can act co-operately with genetic defects to promote carcinogenesis of melanoma. For example, activated PI3K/Akt pathway in obesity may act co-operately with $BRAF^{V600E}$

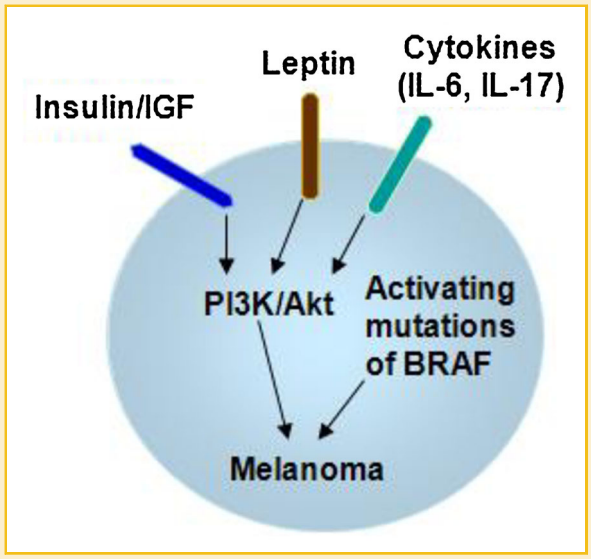

Figure 2. Combinatorial effect of the PI3K/Akt pathway and activating mutations of *BRAF*. A schematic illustration of activation of the PI3K/Akt pathway by increased circulating levels of insulin/IGF-1, leptin, IL-6, and IL-17 in obese individuals may lead to melanoma carcinogenesis with activating mutations of *BRAF*.

to promote carcinogenesis in a similar manner that activated *Akt3* or deficiency of *PTEN* does in other cases (Fig 2). Because multiple signal pathways are activated in obesity, the interactions of these activated pathways with abnormalities in other melanoma risk factors could be complicated.

Recent studies have begun to shed light on the biological mechanisms linking obesity and carcinogenesis of melanoma. In animal models, it has been shown that obesity accelerates the growth of xenografts of B16F10 melanoma cells [Brandon et al., 2009]. This was shown to be related to increased VEGF expression that conceivably activates the PI3K/Akt pathway. Leptin has also been shown to promote melanoma cell growth in mice[Brandon et al., 2009].Leptin-mediated carcinogenesis of other cancers in animal models has been shown to involve activation of the PI3K/Akt pathway [Jaffe and Schwartz, 2008]. In addition, adiponectin has been demonstrated to have preventive effects on melanoma carcinogenesis [Mantzoros et al., 2007]. However, no study has yet reported on the roles of the insulin/IGF-1 axis, IL-6, and IL-17 on melanoma development via obesity, even though these factors have been shown to play roles in obesity-induced carcinogenesis of other cancers, such as colon cancer in mice [Huang and Chen, 2009a,b; Moore et al., 2008].

Obesity-associated activation of the PI3K/Akt has been recently demonstrated in chronic inflammation of skin induced by UV light exposure in mice. Direct evidence was derived from the observation that the PI3K/Akt pathway was activated to a greater extent in skin cells of obese mice than lean ones after exposure to UV light [Sharma and Katiyar, 2010]. Although this study was conducted in non-melanocytic skin cells, the effect of UV light on activation of the PI3K/Akt pathway in obese mice is also implicated in melanoma, as UV-induced chronic inflammation of the skin is considered as an early stage of carcinogenesis of melanoma.

In addition, other signal pathways have been reported to be activated in obesity, including STAT3 and MAPK[Chen, 2011]. These pathways have, in turn, been shown to be involved in several obesity-associated cancers such as liver cancer[Park et al., 2010]. However, these pathways have not been studied in obesity-associated melanoma. It is possible that these pathways are also involved in the carcinogenesis of obesity-associated melanoma. Given that activation of multiple signal pathways is responsible for melanoma carcinogenesis, inhibition of these pathways may have important preventive and therapeutic implications for melanoma in much the same manner as they do for other obesity-associated cancer [Chen, 2012a,b; Chen and Wang, 2012].

As insulin activated PI3K/Akt pathway plays an important role in obesity-associated melanoma. Inhibition of the pathway could be used to prevent and treat obesity-associated melanoma. Metformin not only reduces blood levels of insulin but also inhibit several components of the PI3K/Akt pathway such as mTOR and Akt via activation of AMPK [Wysocki and Wierusz-Wysocka, 2010; Wurth et al., 2013]. Metformin partially inhibited mitochondrial respiratory complex I and thus reduced ATP production and AMPK activation [Pollak, 2012]. Therefore, metformin could be a very effective agent for the prevention and treatment of obesity-associated melanoma and warrants further study. Indeed, metformin has been proved to be effective for the prevention of obesity-associated colon cancer via inhibition of the PI3K/Akt pathway [Algire et al., 2010]. Metformin has also been tested *in vitro* and *in vivo* to inhibit melanoma cell growth [Janjetovic et al., 2011; Tomic et al., 2011] but not studied in obesity-associated melanoma.

mTOR could be highly activated in obesity-associated melanoma as it is activated by both Akt and MAPK. Therefore inhibition of mTOR could be also effective in the prevention and treatment of melanoma. Rapamycin has been used together with Erk inhibitor in NRAS mutated melanoma and proved effectiveness [Posch et al., 2013]. In a phase II clinical trial, mTOR inhibitor everolimus was tested with temozolomide in metastatic melanoma and a small proportion of patients had partial responses[Dronca et al., 2013]. Inhibitors of mTOR could also be tested in obesity-associated melanoma. Dual inhibitors of the PI3K/Akt pathway could have stronger effect as they can inhibit both PI3K and mTOR activity. These inhibitors can eliminate the re-bounce of PI3K/Akt activity caused by inhibition of mTOR[Sznol et al., 2012].

CONCLUSIONS AND FUTURE DIRECTIONS

In summary, the relationship between obesity, multiple signal pathways, and melanoma carcinogenesis is emerging. Further studies are warranted to examine the co-operative effects of activatedsignal pathways resulting from obesity and melanoma related genetic defects. For example, the impact of the activated PI3K/Akt pathway in obesity and activation of the MAPK pathway as a consequence of activating mutations of *BRAF* should be examined in relation to melanoma development. It will also be important to determine if inhibition of obesity-associated signal pathways results in reduced carcinogenesis of melanoma.

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