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DISSERTATION

The mechanism of sensitivity and resistance of melanoma cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)

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1. INTRODUCTION

1.1. Malignant melanoma

1.1.1 Epidemiology

Skin cancer is the most common type of cancer and accounts for half of all new cancers in Western populations. It occurs often in people with light complexion who had a high exposure to sunlight. Three types of cancer such as basal cell carcinomas, squamous cell carcinoma and malignant melanoma (MM) are often diagnosed cases in dermatological practice. Each of these three cancers begins in a different type of cell within the skin, and each cancer is named for the type of cell in which it occurs. The other skin cancers account for less than 1% of diagnosed cases and include Merkel cell carcinoma, dermatofibrosarcoma protuberans, Paget's disease and cutaneous T-cell lymphoma.

Malignant melanoma is the most aggressive skin cancer, which develops through malignant transformation of melanocytes. The number of MM cases worldwide has increased faster than any other cancer in recent decades. In Australia, MM is the fourth most common cancer among males (after prostate, bowel and lung cancers) and the third among females (after breast and bowel cancers) and accounts for about 50 new cases per 100,000 population each year (Diepgen and Mahler 2002). In the U.S.A., the incidence of malignant melanoma has been steadily increasing for the past few decades. For instance, in 1935 the lifetime risk of developing MM was 1 in 1.500 individuals, while in 2002, the risk was 1 in 68 individuals (Rigel 2002). In Europe, MM is the 17th most commonly diagnosed cancer in males and eighth in females. Approximately 26,100 males and 33,300 females were diagnosed with MM in Europe in the year 2000 (de Vries and Coebergh 2004). The highest incidence rates have been reported in Scandinavia (about 15 per 100,000 inhabitants per year) and the lowest in the Mediterranean countries (about five to seven cases per 100,000 inhabitants per year) (Garbe and Blum 2001). The increased melanoma incidence is likely due to changes of lifestyle in terms of extreme exposure to sunlight (Brochez and Naeyaert 2000).

High mortality rates due to tumor progression (metastasis) are the major problem of MM. In parallel, mortality has been stably increasing throughout the world in recent decades (Diepgen and Mahler 2002). Mortality from MM increased both in young adults (20–44 years) and in middle-aged populations (45–64 years) in most European countries, North America, Australia and New Zealand, with a rate of increase of about 2–4% annually (Bosetti *et al*, 2004). Despite rising incidence of MM, a marked improvement in the 5-year survival rate, from approximately 40% in the 1940s to over 90% by now has been reported (Lens and Dawes

2004). The improvement in survival can be attributed to the earlier detection of melanoma. Active public education campaigns aimed at encouraging earlier detection of melanoma led to the diagnosis of thinner lesions which have a better prognosis (Lens and Dawes 2004).

1.1.2 Melanoma progression

The development of melanoma is multifactorial and appears to be related to multiple risk factors, including fair complexion (skin types I and II), excessive childhood sun exposure and blistering childhood sunburns, an increased number of common and dysplastic moles, a family history of melanoma, the presence of a changing mole or evolving lesion on the skin, and older age.

The sequence of events in which normal melanocytes undergo transformation into malignant melanoma ("melanomagenesis") is poorly understood. A multistep process of progressive genetic mutations is probably involve alteration of cell proliferation, differentiation, and death and may increase susceptibility to the carcinogenic effects of ultraviolet radiation.

Melanoma development and progression pass through several distinct stages. Primary MM may develop from precursor melanocytic nevi (common, congenital, and atypical/dysplastic types), which is the first step, although more than 60% of cases are believed to arise de novo (i.e., not from a preexisting pigmented lesion). Radial growth phase (RGP) of primary melanoma is the next step of MM progression. The cells in this phase are locally invasive but they lack metastatic capacity. In the phase of radial growth, malignant cells can progress to the vertical growth phase (VGP) of primary lesions. In this step, melanoma cells infiltrate and invade the dermis as a large cluster of cells and exhibit metastatic potential. Metastasis to distant organs followed by overgrowth of tumor cells in affected sites is the last step of MM progression (Clark 1991).

1.1.3. Clinical characteristic of early melanoma and classification

Clinically, malignant melanoma can be diagnosed by the typical ABCD criteria:

A) Asymmetry – melanoma lesions cannot be easily divided into two halves with one half looking like the other (Fig. 1a)

B) Border irregularity - the borders of most early melanomas are irregularly shaped (Fig 1b)

C) Color variability - most early melanomas have differences in color ranging from subtle nuances of tans and browns, to areas of black and more rarely red, white (regression) and blue (deeper pigment). Amelanotic melanomas lack the color that is usually seen in pigmented melanomas (Fig. 1c)

D) Diameter - most early melanomas, when they are clinically identified, are more then 6 mm in diameter (Fig. 1d)

In the case of patients with histologically proven melanoma, the ABCD clinical features are found in 91% cases. The diameter parameter cannot be seen as an absolute criterion, as melanoma lesions smaller than 6 mm also occur frequently. In this regard, an important clue for diagnosis, regardless of the actual diameter of the lesion, is a change (increase) in the diameter of a given lesion over time.

Four main types of malignant melanoma have been described, based on clinical and histological criteria:

1. Superficial spreading melanoma (SSM). This is the most frequent form of MM in the Caucasian population and is diagnosed in about 65% of all MM cases. At the beginning, a lesion of SSM is flat and grows horizontally, subsequently its surface becomes irregular as circumscribed infiltrated papules or nodules develop, signaling vertical growth. The prognosis is relatively favorable in early phases (horizontal growth). The risk of metastasis significantly increases when vertical growth and dermal invasion occur.

2. Nodular melanoma (NM). This form of MM shows an early vertical growth with rapid invasion of the dermis, makes prognosis unfavorable even in the early phases.

3. Lentigo melanoma (LM). This clinical form accounts for about 10% of the MM cases and can growth for years or even decades until it develops malignant features. The prognosis of this type is more favorable, as the vertical growth occurs only late.

4. Acrolentiginous melanoma (ALM). This type of melanoma is rare in the white population (5%), but it is the principal form in the dark population. It primarily affects the skin of palms and soles.

5. Other malignant melanomas. These include melanoma of the retina and conjunctivae, as well as oral and genital mucosa. A special concern is the amelanotic MM, which raises great problems in diagnosis. It develops as pink or red nodule, usually on extremities. Its prognosis is worse than in other tumors, most probably due to its late recognition or misdiagnosis. And lastly, in some cases, melanoma metastasis can be diagnosed without evidence of a primary tumor.