"Scientific journey: from Bomirski melanoma to a stress- response system in the skin"

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1. Introduction

When asked to prepare this commentary my first inclination was to write on still novel concept, namely, "A cutaneous equivalent of the hypothalamic-pituitary-adrenal (HPA) axis: evolutionary conservation of a fractal mechanism underlying the response to stress". However, the specific instructions from Dr Pawelek were to make it personal and simple and not formatted as a subject oriented review. I was further directed to tell about my journey into pigment biology, starting from my meetings with Dr Bomirski, the subject of this presentation.

2. Dr Andrzej Bomirski and Bomirski melanoma model.

Having a strong interest in science and becoming aware of Dr Bomirski reputation, I joined his group as a volunteer student to work under his supervision within the limits of tolerance of my University schedule, since I was still a medical student at the Medical University of Gdansk, Poland. Dr Bomirski had developed a highly significant melanoma model comprising a family of transplantable tumors in hamsters [1]. The melanomas were linked by a common origin but differed in growth rate, differentiation level, metastatic pattern, immunogenicity and karyotype [1-3]. They were derived from a spontaneous melanotic melanoma whose growth rate had gradually increased during serial transplantation in hamsters resulting in the melanotic Ma melanoma that also gained metastatic capacity [1]. Another tumor was a fast growing Ab amelanotic melanoma that arose through abrupt acceleration of growth rate accompanied by a loss of melanin pigment biosynthetic capacity, and a dramatic change in the karotype (tetraploidy vs diploid chromosome number in parental melanotic line); this tumor had decreased metastatic potential, which was later regained during serial transplantations [1, 2]. The MI melanoma was characterized by slower growth rate and lower pigmentation level but higher tyrosinase activity then the parental Ma melanoma [4], and it also showed switch from the eu- to the pheomelanogenic pathway [1, 5].

The Bomirski melanoma became a general model for our studies on the interaction between melanogenesis and cellular metabolism [6-8] and, on the mechanism(s) regulating melanoma differentiation program [9-11]. The latter was in fact the subject of my PhD thesis under the direct mentorship of Andrzej Bomirski.

3. Dr John Pawelek, his laboratory and my fellowship at Yale University

The next step in my scientific journey was the consequence of a visit to Gdansk of John Pawelek in 1983. First he visited Bomirski laboratory, and latter with his family we visited Lech Walesa house. This was shortly after Lech got the Peace Nobel Price. Because of my involvement with Solidarity movement I had to emigrate to the USA in January 1985 to continue my work in Pawelek's laboratory. Shortly thereafter, using the Bomirski melanoma models we characterized the function of L-tyrosine and L-DOPA as inducers and regulators of the melanogenic pathway and MSH receptors [12-14]. Further

analysis of this phenomenon led us to propose that L-tyrosine and L-DOPA can act as hormone-like bioregulators via a receptor mediated mechanism [15, 16], and that melanocytes can act as both sensory and regulatory cells of the epidermis [17]. It was also in New Haven that I met my future wife Elizabeth, and our wedding ceremony took place in Pawelek's house (Figure 1); and, later my son Radomir Matthew was also born there.

Figure 1. Wedding in Pawelek's house in April 1986.From the left John, myself, Elizabeth and her cousin Theresa.

I completed my scientific training under the supervision of Drs Aaron Lerner and Gisela Moellmann and then moved to establish my independent research laboratory.

4. POMC and CRH signaling systems in the skin.

I had first laboratory at the Toolan Cancer Center in Bennington Vermont, and later at the Albany Medical Center. I also joined my research efforts with those of Ralf Paus, Joseph Mazurkiewicz and Jacobo Wortsman to study the expression and function of the classic hypothalamic and pituitary peptides CRH and POMC in the skin [18-24]. Soon afterwards we had the first article on hair cycle dependent POMC expression in mouse skin, the initial full documentation of the POMC expression in mammalian skin [25]. These studies have now been further extended to the uncovering a cutaneous corticogenic system [19, 22, 26-28]. Together with Martin Mihm (my mentor in dermatopathology) we collected available information and proposed that the skin is expressing a local organizational equivalent of the hypothalamic-pituitary-adrenal (HPA) axis, addressed at counteracting stress and maintaining local homeostasis [26]. This concept has evolved over the last decade and is undergoing continuous testing [19-21, 24, 29-32], with a mechanistic integration of the site action of the main skin stressor, ultraviolet radiation

(UVR) [26, 33-37]. The latter will include identification and characterization of the specific cutaneous UVR receptors originally proposed by John Pawelek [33, 36].

5. Cutaneous neuroendocrine system

Based on the accumulating new evidence together with Jacobo Wortsman we have proposed that the skin, in addition to its barrier function, operates as highly organized neuroendocrine system aimed at regulation of local and global homeostasis via humoral, cellular and neuronal pathways [22]. This endocrine system is structurally organized along the same "chain of commands" as the regulatory axes expressed at the central and/or systemic levels [38].These regulatory organizations comprise not only the HPA axis, but also local catecholaminergic [39], cholinergic [40], serotonin/melatoninergic [41, 42], corticogenic and secosteroidogenic systems [22, 28, 43]. They may also include elements of the hypothalamo-pituitary-thyroid axis [44] and the biosynthetic system of vitamin B6 [45]. This expression patterns raised the possibility that many of these elements may have originally developed in the periphery to be later adopted by a central (systemic) structure as optimal algorithms for control of the interaction between a changing environment and the need to maintain body homeostasis [38].

6. Conclusion

The milestones in my scientific journey are represented by my extremely fortunate experiences of having worked under the supervision of Andrzej Bomirski (he died on January 18, 2002) and John Pawelek. These events solidified my interest in the pigmentary system. The system that indeed serves critical role in the skin by itself, and as a component of a neuroendocrine/stress response system [17, 29].

7. References.

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