ONCOLOGY

Androgen Metabolism in Malignant and Benign Bone Tumors

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The comparison of activities of the key enzymes of androgen metabolism in morphological variants of bone sarcomas and benign tumors suggests that malignant tumors of different histogenesis not only metabolize the main androgen testosterone, but also inactivate 5α-dihydrotestosterone, the main regulatory androgen in bones. It is possible that androgen metabolism in bone tumors is aimed at the formation of other androgens, in particular, 3α- and 5β-diols, which can be involved in regulatory processes in bone tissue. Further studies will disclose clinical significance of androgen metabolism and individual androgens in human bone tumors.

Key Words: *bone tumors; androgens; metabolism*

Androgen metabolism in osseous diseases has been studied for a long time, but physiological role of androgens in the regulatory processes in bones, particularly in blastomogenesis, is still unclear [3,9,11]. Some bone tumors are associated with hyperandrogenemia [2]. This suggests that the development of bone tumors is mediated by enhanced biosynthesis of sex steroids, in particular androgens, or that androgens are released by tumors. The latter implies not only the presence of metabolic enzymes and androgen receptors (AR) in bone tissue and the involvement (direct or indirect) of androgens in the regulation of certain functions in these tissues, but also possible impairment (alteration) of regulatory processes in some osseous diseases, namely in sarcomas.

The data on androgen metabolism in bone tissues are contradictory, but some authors demonstrated the presence of AR in bone tumors [3,13]. All this necessitates comprehensive studies of androgen metabolism in patients with bone sarcomas. When studying the effects of androgen, it is important to detect AR and to assess the role of androgen metabolism and individual metabolites in this tissue.

Metabolism of androgens in a cell is an almost unambiguous evidence of their physiological role in this cell and an indirect indicator of AR. These findings suggest that bone tumors are hormone-dependent, and the possibility of regulating androgen metabolism enzymes as the basis of therapy can be evaluated. It is still more important because contradictory data on androgen metabolism in bone tumors allow no definite conclusions [3].

MATERIALS AND METHODS

The study included 46 patients (aged 15-61 years, primarily males) with malignant bone tumors treated at the Department of General Oncology of Cancer Research Center in 1996-1997. Clinical and x-ray diag-

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nosis was confirmed by histological findings in all patients. Osteogenic sarcoma was detected in 19, chondrosarcoma in 10, Ewing's tumor in 5, giant-cell tumor in 7, and benign tumors in 5 patients.

Testosterone (T) and 5α-dihydrotestosterone (DHT) metabolites were measured in bone homogenates as described previously [7] with modifications. The tumor obtained during surgery or biopsy was minced in liquid nitrogen, suspended in Na phosphate buffer (pH 7.4), and centrifuged at 5000*g* with cooling. The supernatant (total homogenate) was incubated with T or DHT in final concentrations of 10^{-7} mol/liter (with indicator concentrations of ^{3}H-T or ^{3}H-DHT). Enzyme activities were estimated from the content of corresponding metabolites formed in total homogenate per 1 mg protein during 1-h incubation: 5α-R by the formation of the sum of DHT, 3α-D, and 3β-D from T; 17β-HSR activity by the formation of A4 from T; activity of 3α-HSR by the formation of 3α-D from DHT; 3β-HSR by the formation of 3β-D from DHT; and 6,7-HSR by the formation of polar metabolites (compounds with chromatographic mobility lower than that of 3β-D during separation of metabolites) from DHT. The significance of differences was evaluated by Student's *t* test.

RESULTS

No significant differences in the activity of 5α-R in tumors were detected. In some tumors no formation of DHT from T was noted, but other 5α-reduced metabolites were present. In addition, these tumors exhibited high 3α-HSR and 3β-HSR activities (Table 1).

Activity of 17β-HSR was much lower than activities of other enzymes. In Ewing's tumor 17β-HSR activity differed significantly from that in osteogenic sarcoma (p=0.03) and giant-cell tumor (p=0.01).

Activity of 3α-HSR in all tumors was higher (in some tumors significantly higher) than activities of other androgen metabolism enzymes (Table 1). In chondrosarcoma and Ewing's tumor, 3α-HSR activities differed significantly (p=0.05) between themselves and from 3β-HSR activities (p=0.0002).

When tumor homogenates were incubated with DHT, the formation of polar metabolites was observed in the majority of tumors; chromatographic mobility of these metabolites was lower than the mobility of the most polar androgen studied. In some human and animal tissues, 3β-D can be converted into trioles; judging from their structure, the chromatographic mobility of these compounds (in thin layer of silica gel) is expected to be lower than that of 3β-D. We therefore believe that DHT in bone tumors is converted into trioles, because 3β-HSR activity in these tumors is high (Table 1). Presumably, activities of enzymes involved in the formation of trioles reflects the total activity of 6ε,7ε-HSR. However, 6,7-HSR activity did not significantly differ in different tumors and the formation of trioles was observed not in all tumors.

Hence, the major enzymes of androgen metabolism are expressed in bone tumors of different histological structure, but their activity different considerably.

It is noteworthy that 3α-HSR showed the highest activity in the majority of tumors, but other scientists did not detect this enzyme in normal human bone tissue [14].

Published reports and our findings suggest that intense T metabolism in human bone tumors of different origin is paralleled by the formation of DHT

TABLE 1. Activities of Androgen Metabolism Enzymes (fmol/mg Total Protein) in Bone Tumors of Different Histological Structure (*M*±*m*)

Tumor type	Enzymes				
	5α-R	17β-HSR	3α-HSR	6,7-HSR	3β-HSR
Osteogenic sarcoma	2686±537 (14; 570-6624)	98±29 (15; 4-426)	4182±934 (18; 384-15161)	2601±600 (17; 376-9365)	520±106 (16; 70-1674)
Chondrosarcoma	3065±487 (6; 1066-4898)	158±84 (7; 31-658)	3298±1231 (7; 450-9259)	1453±266 (8; 750-2575)	1353±533 (8; 358-3968)
Giant-cell tumor	3235±1550 (5; 788-9281)	59±25 (7; 11-192)	5425±2245 (4; 1149-10906)	3138±403 (4; 2382-4106)	769±426 (3; 96-1558)
Ewing's tumor	2160±860 (5; 786-5004)	421±173 (3; 136-735)	6904±992 (7; 3463-9591)	4094±541 (5; 2587-5407)	1383±700 (4; 79-2860)
Benign tumors	3595±1238 (5; 1475-8410)	124±52 (4; 53-277)	4872±3073 (5; 2632-9348)	2448±1328 (4; 1260-4639)	219±189 (4; 80-485)

Note. Number of tumors and extreme values are shown in parentheses.

(the main regulatory androgen in bone tissue) and other androgens, because hyperandrogenia was detected in many patients with bone tumors [2]. If this is true, androgen metabolism in bone tumors is probably aimed at the formation of other androgens (apart from DHT) which can be involved in bone tissue regulation, in particular 3α-D and 3β-D, whose specific activities are now intensely investigated [1]. The role of androgen metabolism and individual androgens in human bone tumors is still to be studied.

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