



Osteosarcoma Early Detection

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Introduction

Osteosarcoma is the most common primary bone malignancy in children and adolescent. It ranked fifth among all childhood cancer and constitute 35% and 56% respectively of all primary bone malignancy in children and adolescent [1]. In the US alone, about 400 new cases are reported every year from two hundred million plus populations. One fifth of patients reporting to the clinic have already developed metastasis, and about 4 out of 5 resected cases eventually develop metastasis. Despite much improvement in the management of osteosarcoma and the increase in survival rate, the identification of osteosarcoma at its earlier stage is still much desired, which should allow removal of founder sarcoma cells, early enough for virtual elimination of the primary site as well as its metastatic potential.

Unfortunately, almost all cases present to the clinic is already at an advanced stage, with an obvious tumor mass(es) and symptoms of pain [1]. Since early osteosarcoma may not show any obvious symptoms and signs, it is easily confused with common muscle or skeletal complaints, particularly on an apparently healthy subjects as have been reported in many sporadic cases. This does seem to preclude the possibility of early detection of osteosarcoma, there are however, familial syndromes with increase predisposition to developing osteosarcoma [1,2]. Hence early detection should be directed toward these group of patients, where the initiation of osteosarcoma can be detected early prior to development any clinical signs or symptoms.

Familial cancer syndromes have been widely studied for finding of genes that confer susceptibility to oncogenesis [2]. The prototype of its kind is the Retinoblastoma familial eye cancer syndrome, which features bilateral tumor on both eyes at the

very young onset and susceptibility of developing osteosarcoma. Removal of the affected eye(s) unfortunately, is the treatment of choice. In 1971 Knudsen proposed a two hit hypothesis to explain the discordant dominant penetrance of retinoblastoma in probands from a normal and a carrier parents. He proposed that 2 hits or mutations on paternal and maternal copies of cancer genes need to accumulate before Retinoblastoma will develop. In familial cases, a mutated copy is transmitted by one of the parents (first hit), increasing the rate of mutation in the affected tissue of the children as such that it increases the random chances of acquiring mutation on the remaining healthy gene copy (second hit). This hypothesis represents the first multistep oncogenesis model and has been widely adopted for many other familial cancer syndromes. The Advances in molecular genetic analysis and diagnostic have taken forward the model to include multiple genes and pathways in Oncogenesis.

Multiple oncogenic pathways 3 may be simplified into two groups, a group of pathways which transform normal cell to become benign tumor cells, and those that transform benign tumor into malignant cells. Included in first group are genes in the RB/cell proliferation and the P53 (Apoptosis) pathways, while the telomeric, the angiogenic and metastasis pathways are the ones belonging to the latter. On top of these two groups, is the genomic instability pathway, which works to accelerate the mutations rate (instability) of the genome promoting rapid accumulation of mutation of both copies of oncogenic pathway genes.

The Rb/Cell Cycle Pathways [4,5]

The commitment to cell division, rest with the E2F protein, which activate downstream DNA synthesis genes. During resting

phase E2F is inactivated through dimerization by Retinoblastoma (Rb) protein into an inactive complex. The stability of the complex, hence the stability of E2F inactivation, is modulated by the Cyclin Dependent Kinases (CDKs) and the Cyclins. Dimerization by Cyclin activates CDKs to phosphorylate RB within the RB-E2F complex, releasing E2F. The release of E2F activate DNA synthesis genes and commit cell to duplication. The genes encoding Rb is hence called tumor/cancer suppressing genes (TSG), and those encoding Cyclin and CDKs is called cancer promoting genes (oncogenes).

Apoptosis Pathways [5-8]

At the center of Apoptosis pathways during cell duplication is the protein P53. In the presence of DNA damages, P53 will increase in abundant and mediate the halt cell cycle progression through p21 protein, allowing DNA repair machinery to repair DNA damages. If somehow damages are too overwhelming, P53 directs the replicating cell to undergo apoptosis through the activation of BAX protein, leading to degradation of mitochondria, nuclear fragmentation, cell fragmentation and subsequent phagocytosis. P53 activity however, is modulated by several genes; MDM2 provides a negative feedback for P53, decreasing its production, P14 ARF represses MDM2, positively modulating P53, and MYC antagonized G1-S halt but curiously promoting apoptosis at the same time. The genes of P53, P21, P14Arf are regarded as tumor suppressor, while Bcl2, Myc and MDM2 are considered oncogenes.

The Telomeric Pathways [9-11]

The growth advantage, bestowed by perturbations of the RB and the P53 pathways, allows heighten and continuous cell proliferation. Proliferation will eventually stop at some point. Due to the progressive shortening of the chromosomal ends (the telomeres) diminishing the protection against chromosomal erosion. Cancer cells acquire means to maintain or to extend the telomeres by activating the telomerases system or the alternative telomere maintenance pathway (ALT). particularly interesting, is that ALT pathways is mediated to certain aspect by the increased homologous recombination potential facilitated by genomic instability.

The Angiogenesis and Metastasis Pathway

Pertaining to early detection, these two pathways are considered advance and will not discussed. Their involvement would mean that metastases had already been taking place.

The Genomic Instability Pathways [8,12,13]

Theoretically, the very low mutation (instability) rate of the human genome shall not permit the acquisition of inactivating mutations of both copies of each genes in the oncogenic pathway during its life span, yet, sporadic cancer do occur. Apparently, sporadic cancer is attributed to the defect(s) already going-on in the background that enhance the instability rate of the genome. Genes have been shown to be mutated that responsible for increased instability rate includes the WRN (Werner syndrome gene) BLM

(Bloom syndrome gene) and RECQL4 (Rothmund-Thompson syndrome gene) [12,13]; all encodes for proteins functioning in DNA repair.

Genes Belonging to Each Oncogenesis Pathway are Perturbed in Osteosarcoma

Accumulating evidences have shown that genes belonging to each of the oncogenesis pathways are involved in osteosarcoma. Inactivation to tumor suppressor P53, 8, P14ARF5-7 (Apoptosis Pathway), RB4, 5 (RB pathway), BLM, WRN and RECQL413 (Genomic Instability pathways) along with reactivation of oncogenes MDM2, 14, c-MYC15(Apoptosis pathway), CDK46, 14, CYCLIN D (RB pathway), and ALT (telomeric pathway) were among features of osteosarcomas studied this far, in addition to the angiogenesis and metastasis pathway genes.

Based on available evidences, it has been proposed that there are at least 3 phases of osteosarcomagenesis; the early phase which features acquisition of growth advantage to osteoblasts through the perturbation of P53 and RB pathways, the initiation phase, at which cell acquire limitless replicative potential through the activation of ALT pathway for telomere maintenance, and the progression phase, at which the angiogenic and metastasis capability are acquired. Accordingly, early detection may then be directed toward intervening with osteosarcomagenesis at the two earlier phases.

Possible Early Detection Work Up and Follow Up of a Suspect Cases

Early detection is sensibly directed at detecting its emergence in patients with hereditary syndrome with increased osteosarcoma predisposition [2]. One or more of several osteosarcoma pathways often are already perturbed in these patients, developing osteosarcoma is just the matter of accumulating the right combination of additional pathways. For example, the RB pathways is already perturbed in patients with familial Retinoblastoma, the P53 pathway is already perturbed in patients with Li-Fraumeni syndromes, the genomic instability pathways are already perturbed in patients with Thomas- Rothmund syndromes [12].

In the clinics, early detection translates into routine monitoring of the progression of pathways perturbation. 3 phases are envisioned, the identification of predisposed groups, the initial genomic survey, and the routine follow up. Once predisposed groups are identified, cytogenetics work-up is prescribed for capturing the initial karyotype snapshot as a starting microscopic monitoring point. For any chromosomal aberration, genes affected as well as the pathways they belong to is recorded, and probability of developing osteosarcoma are determined. Based on the predisposition, follow up are prescribed, which may simply be a regular cytogenetics examination or molecular genetic analysis. Progression of chromosomal aberration affecting chromosome known to harbor TSGs or Oncogenes is a warning for possible osteosarcoma initiation. Patients should be cautioned of the possibility and be prescribed more advance preventive workup, which include determination of

genes affected by molecular genetics and epigenetics workup and determination of the presence of hot spots of bone growth by bone scan. Appropriate measures to eliminate focus/foci are then carried out preemptively, by chemotherapy solely, or in combination with surgery.

In the absence of progression during routine cytogenetics examination, if permitting, genetic work-ups to survey cytogenetically unaffected pathways genes/chromosomes are recommended. This include the detection defects which may be missed by cytogenetics, such as detection of limited genomic deletion by southern blotting, detection of single point mutation by SSCP, transcript detection by RTPCR (Reverse Transcribed Polymerase Chain Reaction), detection of promoter methylation by methylation sensitive southern or PCR. These should provide comprehensive picture of pathway genes perturbation.

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