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SHORT COMMUNICATION

Oncogenes – the basics

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Normal cell cycle and cell proliferation are regulated by several genes which can be broadly classified into 4 groups viz, proto-oncogenes, tumor suppressor genes, genes regulating apoptosis and genes involved in DNA repair. These genes may be defective due to different factors. The defective genes may lead to production of abnormal proteins which may lead to disruption of the normal cell cycle and proliferation. A single precursor cell with defective gene proliferates surpassing the normal physiologic regulatory process and leads to tumor formation, so, traditionally,it is said that “tumors are clonal” [1-3].

Proto-oncogene is a normal gene, which turns defective due to chromosomal rearrangements (e.g., chromosomal inversions, translocations etc), mutations, or gene amplifications and leads to the formation of “oncogenes”. These oncogenes function autonomously and encode defective proteins with erroneous function which affect the cell regulation in a detrimental way. Usually the encoded protein has excessive normal function or acquires a new function. That is why, these mutations are also called as “gain of function” mutations. Similarly, mutations in tumor suppressor genes also alter the normal cell proliferation but these mutations cause “loss of function” of the encoded proteins. The third group of genes which regulate apoptosis, after mutation, causes inhibition of apoptosis leading to increased survival of the cells. The last group of genes which repair any accidental defect in the DNA during cell division may lose their normal function once they are mutated [1]. Mutations can be in the germ line and thus hereditary or they can be acquired due to known (e.g., environmental factors , viral infections) or unknown causes. In carcinogesis, most of the mutations are of acquired type [4].

As it was mentioned, oncogenes (the altered activated proto-oncogenes) lead to encoding of defective proteins which are known as oncoprotiens. These oncoproteins affect the normal cell cycle and enhance the proliferation of the cells. Normally cell proliferation includes a multistep sequential process involving several proteins and interestingly, oncogenes can affect any or several of these steps. In normal physiologic cell proliferation, growth factors bind to growth factor receptors on the cell surface leading to activation of several intracellular signalling pathways in the cytoplasm, which in turn induce and activate regulatory proteins in the nucleus. These activated nuclear factors initiate DNA transcription [1, 3].

Table - 1 Examples of a few oncoproteins, its types and related malignancies [1, 5]

Type		Oncogene	Related Malignancies
Growth factor	PDGF – β	PDGFB	Astrocytoma
	Fibroblast growth factor	FGF3	Stomach, Urinary bladder, Breast carcinomas, Melanoma
Growth factor receptor	EGF receptor	ERBB1 (EGFR)	Adenocarcinoma of Lung
	EGF receptor	ERBB2 (HER)	Breast carcinoma
	Receptor for neurotrophic factor	RET	Familial medullary thyroid carcinoma
	PDGF receptor	PDGFRB	Glioma, Leukemia
	Receptor for KIT ligand	KIT	Gastrointestinal stromal tumor(GIST)
	ALK receptor	ALK	Adenocarcinoma lung, certain Lymphoma, Neuroblastoma
Signal transduction pathway	GTP binding protein	KRAS	Colon, Lung, Pancreas carcinoma
	Tyrosine kinase	ABL	Chronic myelogenousleukemia(CML), Acute lymphoblastic leukemia (ALL)
	RAS signal transduction	BRAF	Melanoma, Leukemias
	JAK/STAT signal transduction	JAK2	ALL, Myeloproliferative disorder
Nuclear regulatory protein	Transcriptional activator	MYC	Burkitt lymphoma
		NMYC	Neuroblastoma
Cell cycle regulator	Cyclin	Cyclin D1	Mantle cell lymphoma, Multiple myeloma
	Cyclin dependent kinase	CDK4	Gliobllastoma, Melanoma

There are several subtypes of growth factors, surface receptors, proteins involved in intra-cytoplasmic pathways and intra-nuclear proteins. These processes ultimately lead to progression of a cell in the cell cycle and further cell division. Cell cycles are regulated by cyclins, cyclin dependent kinases and inhibitors. As the above multistep processes involve several subtypes of proteins or factors, mutated protein counterparts or oncoproteins too can be of several subtypes and lead to increased number of mutated cells [1-3]. Oncoproteins can also affect other processes besides cell cycle, e.g., angiogenesis in tumor, metastasis etc. [1]. Some of the oncogenes, its type and the related cancer have been depicted in Table 1 [1, 5].

The initial genetic alteration "initiates" the process of tumor formation or carcinogenesis. It was seen in experimental models as well as in some malignancies that tumors may behave differently with time, for example, it may become suddenly aggressive or the response to the treatment regimen may change. It led to the hypothesis that during progression of the tumor, the cells acquire additional genetic alterations which lead to formations of subclones of tumor cells [3, 4]. The traditional concept was that the initial genetic alteration may affect a normal cell which is already differentiated, while the recent concept indicates that stem cell or progenitor cells are the first target [6]. Most hematopoietic tumors and soft tissue sarcomas are initiated by activation of an oncogene, followed by alteration in tumor suppressor genes and other oncogenes. In contrast, most carcinomas are initiated by loss of function of tumor suppressor genes followed by alterations in oncogenes and additional tumor suppressor genes [4].

Significance of oncoproteins includes diagnosis and assessment of prognosis of different types of tumors as well as in therapeutics. Some of the drugs, its targets and uses are depicted in table 2 [4].

Table - 2 A few examples of therapeutic drugs and related oncogenes [4].

Drugs	Oncoprotein	Related malignancies
Trastuzumab (Herceptin)	ERBB2 (HER)	Breast
Cetuximab	EGFR	Colorectal
Imatinib (Gleevec)	ABL, KIT, PDGFR	CML, GIST
Gefitinib	EGFR	Lung (non small cell carcinoma)
Erlotinib	EGFR	Lung (non small cell carcinoma)
Sorafenib	VEGFR, PDGFR, FLT3	Renal cell carcinoma(RCC)
Sumatinib	VEGFR, PDGFR, FLT3	RCC, GIST

Carcinogenesis is an evolving subject with many ongoing researches across the globe, ever changing concepts and upcoming literature. The very basics and traditional concepts of oncogenes have been outlined in this communication. Interested readers may further build their knowledge by reading more specialized literature.

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