CHAPTER 17

NOTCH AND THE p53 CLAN OF TRANSCRIPTION FACTORS

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Abstract: Notch 1 to 4 and the p53 clan, comprising p53, p63 and p73 plus numerous isoforms thereof, are gene transcription regulators that are critically involved in various aspects of cell differentiation, stem cell maintenance and tumour suppression. It is thus perhaps no surprise that extensive crosstalk between the Notch and p53 pathways is implemented during these processes. Typically, Notch together with p53 and even more so with transactivation competent p63 or p73, drives differentiation, whereas Notch combined with transactivation impaired p63 or p73 helps maintain undifferentiated stem cell compartments. With regard to cancer, it seems that Notch acts as a tumour suppressor in cellular contexts where Notch signalling supports p53 activation and both together can bring on its way an anti-proliferative programme of differentiation, senescence or apoptosis. In contrast, Notch often acts as an oncoprotein in contexts where it suppresses p53 activation and activity and where differentiation is unwanted. It is no accident that the latter pathways—the inhibition by Notch of p53 and differentiation—are operative in somatic stem cells as well as in tumour cells.

INTRODUCTION

The Notch and p53/p63/p73 proteins (the p53 clan hereafter) all function typically as receptors/sensors-that-turn-into-transcriptional-regulators-upon-stimulus, with the main difference being that Notch senses signals at membrane surfaces through contact with membrane anchored ligands while the p53 clan, mostly in the nucleoplasm, responds to a large and still growing number of alterations in cell homeostasis commonly referred to as stress. In any event is the result of such activation—manifested by specific cleavage processing (Notch) and chemical modifications and oligomerization (the p53 clan)—the
contact with regulatory DNA. This contact is indirect through association with a DNA binding transcription factor in the case of Notch and direct in the case of the p53 family. Finally, in both pathways the cell type and context dependent recruitment of nuclear coregulators entails the stimulation or repression of a very large number, perhaps hundreds, of genes. Several of these code themselves for transcriptional regulators, adding a further level of complexity to the networks. It is obvious that transcription factor pathways may crosstalk, for instance, through the sharing of target genes or coregulators and through the engagement in interdependent regulatory loops. Indeed, all of these mechanisms, plus several others, seem to have been realized in the crosstalk of Notch with the p53 clan.

Conspicuously, both groups of pathways are involved—although at first sight in an antagonistic manner—in the regulation of stem cell maintenance, cell differentiation and cell homeostasis that are at the heart of organismal as well as cancer development. While Notch primarily controls the preservation of stemness and the asymmetric development of cell lineages with divergent fates, some members and isoforms of the p53 clan and in particular p53 itself, by contrast reduce the stem cell potential and stimulate differentiation. This antagonism, however, is not inscribed in stone. In dependence, for example, of coregulator recruitment, Notch signalling may counteract proliferation and support rather than prevent differentiation. On the side of the p53 clan, for instance, all three members can be expressed as truncated isoforms capable of counteracting their siblings’ transactivating effects. Altogether, the presently available data clearly point to the crosstalk of Notch and the p53 clan being intricately entangled in cell lineage decisions as well as in tumourigenesis. The present chapter intends to provide an overview on this interesting signalling network. But before the crosstalk is discussed, the pathways should be outlined individually.

NOTCH

Notch 1 to 4 are highly homologous single pass transmembrane receptors on the surface of signal receiving cells that can become activated upon contact with one of five canonical Notch ligands (Jagged 1 and 2; Delta-like 1, Dll 3 and 4 in mammals), or one of several noncanonical ligands, on the surface of neighbouring signal emitting cells. Ligand/receptor interactions within the same cell inhibit rather than induce Notch signalling; both the activating and repressing interactions have physiological relevance. Importantly, expression of ligand/receptor is necessary but insufficient for productive signalling, as is evidenced for instance by an often only very sparse, spatio-temporally limited, signalling activity despite of ubiquitous ligand/receptor expression in some tissues. This and the fact that Notch signalling can elicit many different responses already points to a complex regulation of this pathway and a need for integration of many additional signals that goes way beyond a simple canonical ligand/receptor triggering of gene expression. It is now appreciated that Notch signalling involves the coordination of several posttranslational modifications including, but not limited to, activating endocytosis-inducing ubiquitination of the ligand, activating glycosylation and chaperone contact of the receptor, activating proteolytic cleavages of the receptor and inhibiting ubiquitinations of the receptor such as those by the E3 ubiquitin ligase Numb. Activating ubiquitinases affecting the ligand and inhibiting ubiquitinases affecting the receptor can cosegregate in asymmetric cell divisions and thereby support the formation of disparate daughter cells. Altogether, chemical modifications to the Notch pathway control such critical