

The Head of Janus: Exploiting Autophagy for Cancer Therapy

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Macroautophagy (hereafter referred to as autophagy) is a complex, multi-step process normally involved in regulated turnover of long-lived proteins and damaged organelles. Autophagy is a form of cellular self digestion in which cellular constituents are engulfed in double-membrane containing autophagosomes. Their vesicular content is subsequently digested by lysosomal proteases after fusion of autophagosomes with lysosomes. In recent years, elucidation of the physiological and pathophysiological aspects of autophagy and the identification of key components of the autophagy interacting network has generated a tremendous interest in the concept of exploiting autophagy for cancer therapy [1-4].

What is the common rationale of targeting autophagy for cancer therapy? The net effects of autophagy on cell death/cell survival decisions are highly dependent of the cellular context and hence autophagy may have dual, opposing roles [5]. It is now widely accepted that autophagy primarily constitutes a quality control mechanism and a pro-survival stress response, e.g. under conditions of nutrient deprivation, organelle damage, oxidative stress or after DNA damage [6]. In line with this hypothesis, there are numerous examples and experimental paradigms where pharmacological inhibition or genetic ablation of pro-survival autophagy can sensitize cancer cells to various types of therapy [7,8]. On the other hand, there is also evidence supporting the notion that enforced over activation of autophagy can lead to “autophagic cell death” (type II cell death), i.e. massive cellular self digestion via the autophagosomal-lysosomal pathway beyond the point allowing cell survival. This could be especially relevant in apoptosis-resistant cells such as glioblastoma cells, where autophagy may act as a backup cell death mechanism executing a non-apoptotic, alternative death program [9,10].

However, this is a controversial, hotly debated issue [11,12] and the very existence of autophagic cell death has been challenged recently [13]. Indeed, in many paradigms of cell death associated with induction of autophagy, autophagy may just act as a bystander without a direct role in the death process. In line with this notion, many of the past studies on “autophagic cell death” did not really investigate the pro-death function of autophagy and therefore do not fulfil the current, more stringent criteria that recently were suggested to be applied for autophagy-dependent cell death [5,11].

Despite this ongoing controversy regarding the pro-death role of autophagy, there are a number of experimental studies suggesting that pro-autophagic drugs may elicit an autophagy-dependent cell death in certain cases [8]. In addition to these findings on drug-induced autophagic cell death in mammalian cells, there is also considerable evidence for autophagy-dependent developmental cell death in *Drosophila* [14,15]. Therefore, the issue of autophagy as a cell death mechanism in general and the ensuing therapeutic consequences for cancer therapy warrant further examination in order to determine whether activation of autophagy may indeed have significance for therapy, especially in apoptosis-refractory tumors.

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