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Obituary

Jürg Tschopp—1951–2011—an immortal contribution

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A shockwave has shaken the cell death community. Jürg Tschopp, a *CDD* editor, suddenly and unexpectedly died at the age of 59 while ski touring with his son in the Swiss Alps. His family, friends, colleagues and the entire community of cell death researchers deplore a tragic loss.

Jürg Tschopp received his PhD in biophysics at the University of Basel in 1979. As a postdoctoral fellow, he joined the group of Müller-Eberhard at the Scripps Clinic in La Jolla. In 1982, he was appointed assistant professor at the Department of Biochemistry of the University of Lausanne, where he was promoted to the rank of full professor only 7 years later, in 1989. Since 2003 he has been deputy-director of the Department of Biochemistry. In 2008, he won the most important Swiss biomedical research prize, the Jeantet Prize (see web link below). Jürg Tschopp also won the Novartis Clinical Immunology Prize 2010, the European Cell Death Organization (ECDO) Award 2006, the San Salvatore Cancer Award 2004, the Max Cloëtta Prize 1992 and the Friedrich Miescher Prize 1986 for his outstanding achievements.

Jürg Tschopp started his career in the cell death field very early, driven by his interest in how immune effectors can kill cells. Accordingly, he characterized the mechanisms through which complement factors can permeabilize cell membranes[1,2] and how cytotoxic T lymphocytes mediate cytolysis, discovering the mechanisms through which perforin polymerizes in target cell membranes.[2,3] He then discovered that T-cell cytotoxicity can be mediated through alternative, perforin-independent pathways that involve the ligation of CD95/Fas on target cells.[4] He soon realized that tumor cells can express the CD95/Fas ligand on their surface and can subvert anticancer immunosurveillance by engaging the CD95/Fas receptor expressed on the surface of immune effectors including T cells.[5] Based on these results, he developed a deep interests in the lethal signals transmitted upon ligation of CD95. Jürg Tschopp was the first to discover that viruses that are pathogenic for mammals can encode caspase inhibitors, hence describing a family of viral caspase-8 inhibitors, dubbed 'FLIPs', that are present in several g-herpesviruses (including Kaposi's sarcoma-associated human herpesvirus-8) and the tumorigenic human molluscipoxvirus.[6] Viral FLIPs turned out to have a cellular equivalent, which was called cellular FLIP that prevents lethal CD95 signaling by interacting with FADD and so avoiding activation of caspase-8.[7] The expression of FLIP has turned out to have a tremendous impact on the homeostatic regulation of normal tissues and immune responses, and its overexpression may contribute to the notorious resistance of cancer cells to cell death induction.

Jürg Tschopp's work also led to the first description of RIP1, which, as he described more than 10 years ago, can mediate an alternative, caspase-8-independent cell death pathway upon ligation of CD95/Fas.[8] Since then, RIP1 has become an enormously important molecule that has a major role in programmed necrosis and actually defines 'necroptosis', a caspase-independent cell death modality. Pharmacological RIP1 inhibitors actually have an enormous potential for the avoidance of undesirable cell death, for instance in the context of stroke or myocardial infarction.

Jürg Tschopp was also the first to discover that the death-inducing signaling complex that is organized around the TNF receptor 1 when TNF is added to cells modifies its composition over time, switching from a first step (complex 1) that may mediate survival signals (that via RIP1 lead to the NF-κB-dependent expression of FLIP) to another (complex 2) in which the presence or absence of FLIP determines whether the cells survive or activate a lethal caspase activation cascade.[9]

After these important contributions to the understanding of the extrinsic pathway of apoptosis, Jürg Tschopp became interested in novel caspase activation platforms. He discovered PIDD that upon genotoxic stress can either mediate lethal caspase-2 activation (when PIDD interacts with RAIDD to form the PIDDosome)[10] or cytoprotective NF-κB activation (when PIDD interacts with RIP1 and NEMO).[11] He also unraveled the pathophysiological importance of the NLRP3 inflammasome, the caspase-1 activation complex that results in the post-translational maturation and secretion of several inflammatory cytokines including IL-1β and IL-18. Thus, he showed that gout-associated monosodium urate crystals and pseudogout-associated pyrophosphate dihydrate crystals can stimulate activation of the NLRP3 inflammasome,[12] establishing the pathophysiological bases of gout (or pseudogout)-associated inflammatory reactions. Subsequently, Jürg Tschopp demonstrated the general importance of caspase-1 activation cascades for the initiation of innate immune response by cytosolic DNA, be it from microbial or

host origin.[13] Similarly, he found that NLPR3 inflammasome activation could be triggered by asbestosis or silica particles.[14] As a common pathogenic principle, he discovered that multiple inflammation-inducing conditions caused the production of excessive reactive oxygen species by mitochondria, resulting in the activation of the NLRP3 inflammasome.[15]

Beyond these fundamental insights into basic biological principles, Jürg Tschopp's work laid the groundwork for the treatment of several major diseases. Indeed, his discovery that IL-1β activation via the NLRP3 inflammasome can drive the pathogenesis of major inflammatory pathologies (including gout, type 2 diabetes and hereditary auto-inflammatory diseases) led to the launch of several highly encouraging clinical trials showing that the neutralization of IL-1β can attenuate the symptoms of this kind of disease. Thus, it appears more than plausible that Jürg Tschopp's work has laid the theoretical and practical grounds for treating several major, socioeconomically important diseases.

Despite his widely appreciated position in the scientific world (on the day of his death he had an *h* index of 105 and his work had been cited 41 980 times according to the Science Citation Index), he was a humble, accessible and amiable person. Jürg Tschopp demonstrated that a combination of passion, vision, organization, perseverance and didactic skills may leave an immortal legacy. As laymen, patients, and scientists we thank Jürg for his outstanding contribution to science and medicine. In recognition of Jurg's outstanding contribution to the cell death field, we intend to devote a future issue of *CDD* in his memory.

Recent interview (French) with English subtitles:
http://www.jeantet.ch/e/prize/CLIP_TSCHOPP.html

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1. Tschopp J *et al. Nature* 1982; **298**: 534–538.
2. Tschopp J *et al. Nature* 1986; **322**: 831–834.
3. Tschopp J *et al. Nature* 1989; **337**: 272–274.
4. Lowin B *et al. Nature* 1994; **370**: 650–652.
5. Hahne M *et al. Science* 1996; **274**: 1363–1366.
6. Thome M *et al. Nature* 1997; **386**: 517–521.
7. Irmler M *et al. Nature* 1997; **388**: 190–195.
8. Holler N *et al. Nat Immunol* 2000; **1**: 489–495.
9. Micheau O *et al. Cell* 2003; **114**: 181–190.
10. Tinel A, Tschopp J. *Science* 2004; **304**: 843–846.
11. Janssens S *et al. Cell* 2005; **123**: 1079–1092.
12. Martinon F *et al. Nature* 2006; **440**: 237–241.
13. Muruve DA *et al. Nature* 2008; **452**: 103–107.
14. Dostert C *et al. Science* 2008; **320**: 674–677.
15. Zhou R *et al. Nature* 2011; **469**: 221–225.